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A. LICHTENSTEIN
KRONPRINSESSAN LOVISAS BARNSJUKHUS,
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EDITOR PROFESSOR A. LICHTENSTEIN
KRONPRINSESSAN LOVISAS BARNSJUKHUS,
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HELSINGFORS JUNE 27-JUNE 29, 1946

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Minutes of the Proceedings.

Friday, June 28th, 9 a.m. - 11 a.m.

The President, Prof. A. YLPPÖ (Helsingfors), opened the Congress.

He proposed as Vice Presidents Prof. A. LICHTENSTEIN (Stockholm), Prof. P. PLUM (Copenhagen), Prof. A. WALLGREN (Stockholm), Dr. A. SUNDAL (Oslo), Dr. C. FRIDERICHSEN (Copenhagen), Prof. C. Gyllenswärd (Uppsala), Prof. S. SIWE (Lund) and Dr. V. Rantasalo (Helsingfors), who were all elected by acclamation.

Visit to the new Children's Clinic, Stenbäcksg. 11.

First meeting, Section I, June 28th, 13.30—18.00. Prof. A. Lichtenstein (Stockholm) took the Chair.

The following papers were read:

- Prof. S. Siwe (Lund): Acute gastro-enteritis accompanied with toxicosis in infancy.
- Dr. A. NJA (Oslo): Nosocomial malignant diarrhoea and vomiting in infancy.
- Dr. P. Forssell (Helsingfors): Pyuria in Finnish children, 1933
 —1945.
- Dr. K. Wilken-Jensen (Copenhagen): Treatment of Pneumonia with shock doses of sulphatiazol in 688 cases.
- Dr. B. H. HESSELMAN (Stockholm): Massive single-dose chemotherapy in pneumonia in children.

Papers 1—3 were discussed by the following members: Profs. Lichtenstein and Siwe, Drs. Friderichsen, Gjörup, Rantasalo & Räihä.

- Dr. J. Ström (Stockholm): The breast-feeding of mature infants during the neonatal period, and the influence of some factors on the same.
- Dr. Y. ÅKERRÉN (Gothenburg): Infant mortality in Sweden and in Gothenburg during recent times.
- Drs. B. Roos (Lund) and B. Wahlström (Malmö): The care, in Sweden, of Polish infants born in concentration camps.
- Dr. G. KLACKENBERG (Stockholm): Mental injuries due to hospitalization or custody in children's homes.
- Dr. A. Bojesen (Copenhagen): Child welfare work in Denmark. Discussion by Drs. Rinvik, Ström & Leppo.
- 18.00 Visit to picture theatre to see the film »The future of the new generation».

Second meeting, Section II, June 28th, 13.30—18.00. Prof. P. Plum (Copenhagen) took the Chair.

The following papers were read:

- Dr. N. Faxén (Gothenburg): Factors influencing the risk of complications in scarlet fever.
- Dr. E. G. Jacobsson (Stockholm): On the prognosis of the rheumatic fever.
- Dr. R. Thelin (Lund): Antistreptolysin titer and sedimentation rate in Polyarthritis and Endocarditis in childhood.

Discussion on papers 11—13 by Prof. Plum, Drs. Bojlen, Faxén & Jacobsson.

- Dr. W. RISINGER (Borâs): A summary of 100 cases of tuberculous coxitis.
- Dr. H. Nathorst (Stockholm): Die Tuberkulosefrekvenz nach exsudativen Pleuritis bei Kindern.
- Drs, B. Landtman and T. Salmi (Helsingfors): Studien über kongenitale lues in Finnland. The paper was read by Dr. Salmi.
- Dr. A. Sundal (Oslo): Hormone treatment of the incompletely descended testicle.
- Dr. H.-O. Mossberg (Stockholm): Sella turcica in obesity in Children.
- Dr. B. Hamne (Falun): Three cases of congenital laryngostenosis with different etiologies.

 Dr. A. Arvola (Helsingfors): Follow-up examinations of cases of poliomyelitis.

Discussion on papers 14—17 & 20 by Profs. Wallgren, Plum and Drs. Enkvist, Sundal, Malmberg, Mali & Ström.

Third meeting, Section I, 29th June, 8.30—11.00. Prof. A. Wallgren (Stockholm) took the Chair.

The following papers were read:

- Prof. A. Ylppö (Helsingfors): Proposal for the adoption of a new classification and nomenclature for new-born infants including prematures and abortions.
- 22. Dr. G. ÅGREN (Uppsala): On the chemical properties and clinical use of protein hydrolysates.

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- Dr. G. v. Sydow (Gothenburg): The development of rickets in premature infants.
- 24. Dr. O. Mellander (Uppsala): On the absorption of calcium and phosphorus.
- Dr. S. Vendel (Stockholm): The principle of evacuation of the stomach in infants and prematures.
- Dr. F. Karlström (Karlstad): A case of alimentary fatty liver. Discussion on papers 21—22 & 25 by Profs. Lichtenstein & Ylppö and Drs Heikel, Vendel & Räihä.

Fourth meeting, Section II, 29th June, 8.30—11.00. Dr. A. SUNDAL (Oslo) took the Chair.

The following papers were read:

- 27. Drs. P. Karlberg & J. Lind (Stockholm): Sur la détermination du volume de sang chez l'enfant.
- 28. Drs. E. & M. Vermehren (Copenhagen): A new Vitamin affecting Anæmia in growing animalorganism.
- Dr. S. Axtrup (Lund): The blood copper in anaemias of children.
- 30. Dr. Olga Imerslund (Oslo): Eosinophilia leukaemoides.

31. Dr. O. Elgenmark (Stockholm): The development of the ossific centres in some diseases in early childhood.

Discussion on papers 27—30 by Drs. Ågren, Jalavisto, Vahlqvist & Rantasalo.

Fifth meeting, Section I, June 29th, 13.00—16.00. Dr. C. Friderichsen (Copenhagen) took the Chair.

The following papers were read:

- 32. Dr. E. Mannheimer (Stockholm): Experiences from operated cases of patent ductus arteriosus.
- 33. Dr. L.-E. CARLGREN (Stockholm): Gallop rhythm and myocardial damage in childhood.
- Dr. B. Landtman (Helsingfors): Heart arrhythmias in children. Discussion on papers 32—34 by Prof. Lichtenstein and Drs. Räihä & Mannheimer.
- Drs. P. E. Möller and F. Nörgaard & Prof. P. Plum (Copenhagen) (read by prof. Plum): Roentgenological investigations of the small intestine in coeliac disease.
- 36. Dr. O. Somersalo (Helsingfors): Intravenous and oral glucosetolerance tests relating to patients suffering from celiac disease.
- 37. Dr. A. ØDEGAARD (Oslo): Resorption research on celiac disease.
- 38. Dr. J. Wickström (Helsingfors): Intravenous glucose tests in cases of mongoloidism.
- Dr. L. Gram (Oslo): A case of recurrent vomiting in a child with electrical cerebral dysrhythmia.

Discussion on papers 36—39 by Prof. Plum and Drs. Friderichsen, Palmberg & Ström.

Sixth meeting, Section II, June 29th, 13.00—16.00. Prof. C. Gyllenswärd (Uppsala) took the Chair.

The following papers were read:

 Dr. B. Vahlqvist (Uppsala): Studies on Diphtheria.
 Discussion on paper 41 by Drs. Kjellberg, Wickström & Rantasalo.

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- 41. Dr. E. Rustung (Oslo): Clinical-experimental Investigations on the Absorbtion of Ascorbic Acid with simultaneous Administration of Cod-Liver Oil or Concentrations of A- or D-Vitamine.
- 42. Dr. Annie Schondel (Copenhagen): Studies on the urinary excretion of thiamine in children.

 Discussion on paper 41 by Dr. Sundal.
- 43. Dr. P. J. Nordenfelt (Stockholm): The care and prevention of pes planus in the child of pre-school age.
- 44. Drs. B. Lindqvist & B. Roos (Lund): On injuries to children by corrosive poisons.
- 45. Dr. J. H. Magnusson (Stockholm): An amino acid mixture (casein hydrolysate) as an additional food for premature infants.

General Meeting of the Northern Pediatric Association.

The Meeting was informed and expressed its approval of Dr. Sundal having acted as Secretary-General after the death of the holder of that office, Dr. Johannessen.

The secretaries for the respective countries accounted for the following amounts:

 Danish Crowns
 2.032: —

 Finnish marks
 94.000: —

 Norw. Crowns
 3.529: 53

 Swedish Crowns
 4.640: 51

Dr. A. NJÅ submitted Statement of Accounts for the Seventh Pediatric Congress, audited by Dr. L. Stoltenberg and Prof. L. Salomonsen, which was adopted.

The Meeting was informed that membership fees had not been remitted to the Secretary-General owing to prevailing conditions and currency restrictions. The Congress approved this and resolved that the funds should be administered for the time being by the secretaries in the respective countries.

The Meeting approved the measure taken by the Committees in the separate countries in 1940, by which the membership fees for that year were presented as a gift to the Relief Fund for Finnish children.

The Council's proposal that the ninth Northern Pediatric Congress should be held in 1948 in Copenhagen was adopted. It was decided, on the motion of Dr. Friderichsen, that the Congress should be held as soon as possible after the 15th of August and that it should not take place simultaneously with any nordic congress of internal medicine, tuberculosis or school hygiene or with an international

pediatric congress. The physician-in-chief, Dr. FRIDERICHSEN, Denmark, was elected President.

Dr. Gjörup, Denmark, and Dr. Lahdensuu, Finland, were elected auditors, with Dr. Marvel, Norway and Doc. Malmberg, Sweden, as substitutes.

The annual membership fee was fixed at 15: — crowns, for Finland 600: — marks.

The following proposals for amendment of the statutes were adopted, although they had not been submitted one month before the opening of the Congress, on account of the unsettled times:

It was added to Rule 2 that members of at least twenty years' standing, having paid their annual fee for that period, should not pay any membership fee after attaining the age of retirement for professors in the respective countries.

Rule 3 was amended to the effect that the Council of the Association shall consist of three members and one deputy from each country.

Prof. Th. Frölich and Prof. KJ. AF KLERCKER were elected Honorary Members.

The following executive committees were elected:

For Denmark: Dr. C. Friderichsen, Dr. P. Drucker and Prof. P. Plum, with Prof. O. Anderssen as deputy.

For Finland: Prof. A. Ylppö, Dr. V. Rantasalo and Dr. C.-E. Rähä, with Dr. P. Heiniö as deputy.

For Norway: Prof. L. SALOMONSEN, Dr. L. STOLTENBERG and Dr. A. Njå, with Dr. A. SUNDAL as deputy.

For Sweden: Prof. A. Lichtenstein, Prof. C. Gyllensvärd and Prof. A. Wallgren, with Dr. J. Ström as deputy.

Opening Address.

By

Prof. Arvo Ylppö, M.D., Helsingfors. President of the Congress.

Exactly eight years have gone by since the Seventh Northern Pediatric Congress was held in Oslo. It was then decided that we should next meet in Helsingfors in 1941, but our expectations were not fulfilled. The world-war broke out, bringing dark years and severe trials to all of us. In our country, medical students and physicians were gradually compelled to abandon their work almost completely, and our opportunities of meeting Nordic colleagues were extremely limited.

All the more eagerly do we anticipate exchanging views again, usual and scientific under quieter conditions, and we warmly welcome the opportunity to attend and take part in profitable discussions on war-time pediatric problems, of which our Nordic countries have also had their share.

Here in Finland we have had great misgivings concerning our ability to act as hosts to the Congress so soon after the war and our chances of carrying out this task with honour have seemed very small indeed. During the few hours you have spent in our country you have no doubt noticed that life in Finland has changed very much since pre-war days. Travelling has become more tiring and our means of extending hospitability in the way we should like are extremely restricted.

Nevertheless, we were anxious to invite you to our country now. We wished to make use of the earliest opportunity to manifest the warmth of our hearts and our gratitude towards all of you for having helped and nursed our children with such self-sacrificing noble and untiring love. Also, we were eagerly hoping to hear about, and profit by, the admirable results attained by you in the field of research, and finally we thought that our new Children's Clinic might be of interest, especially in view of the fact that you yourselves are in many places engaged in erecting new hospital buildings. I see already on this occasion that our expectations have not been deceived. In spite of all the inconveniences connected with travelling and all other difficulties due to presentday conditions, you have arrived, almost to a man — I learn with regret that currency restrictions have prevented many of you from bringing your wives — to the Eighth Nordic Pediatric Congress. I bid you heartily welcome.

It looks as if we, Northern pediatricians, have a great deal to say to each other. So many papers have been contributed that we have been obliged to cut down the number of contributions, especially our own. In addition, the meetings have had to be divided into two sections, which is a great pity.

Yet, we miss many faithful friends and members. I specially wish to mention the Honorary Members Adolf Mayer and Wernstedt and also Professors Bloch, af Klercker, Frölich, Thorling, Salomonsen, and Dr. Poulsen. I propose that we send a telegram on this occasion to each of these valued members.

During the past eight years a remarkably large number of the most distinguished members of »Nordisk Pediatrisk Förening» have been taken from us. It is with especially great regret and deep sorrow that I record the death of Prof. Isak Jundell. He was a pediatrician possessed of uncommon and outstanding qualities. His mellow, charming personality harboured a soul of fire which united in common endeavour not only the pediatricians of the North but of the whole world. He was keenly interested in »Nordisk Pediatrisk Förening» and its publication »Acta Paediatrica». He leaves a great gap in our midst. Prof. Monrad's lively and extremely vital figure is also gone, as is Dr. CARL LOOFT'S. Only two months after the last, so very successful, congress in Oslo we were deeply shocked to learn of the death of Dr. Christen JOHANNESSEN, the idolized General Secretary of that Congress. In Dr. Ernberg the Society has lost a skilful pediatrician who participated actively in our congresses, often giving inspiring suggestions. Furthermore, Death has taken our Danish colleague Dr.

Benny Mayer, and we Finns much regret the loss of Prof. Carl Nyberg, Dr. Rikhard Räihä, Dr. Ragnhild Granholm, Dr. Vivan Lagerborg and Dr. Gunnar Ekbom.

I ask the Congress to rise to honour the memory of our deceased $_{\mbox{\scriptsize colleagues}}.$

On behalf of the International Committees I propose that Prof. Th. Frölich, Oslo, and Prof. KJ. af Klercker, Lund, be elected Honorary Members of the Congress.

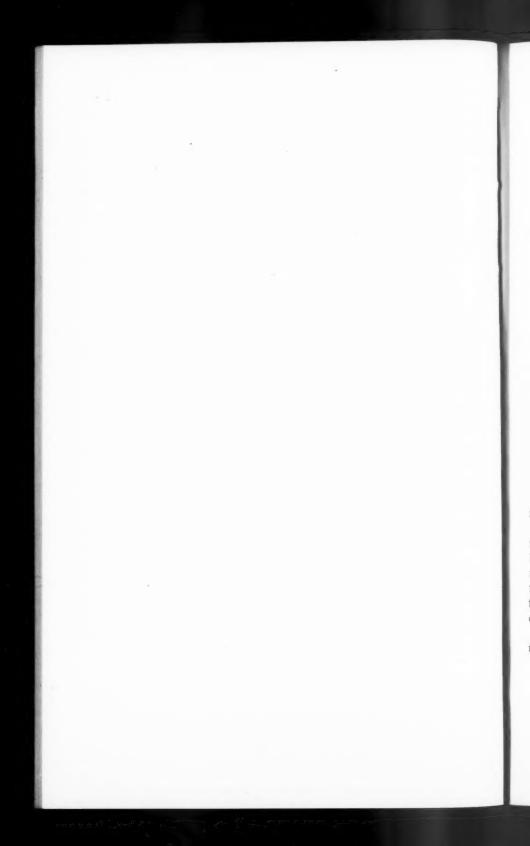
As Vice-Presidents I beg to propose the following:

Prof. A. LICHTENSTEIN.

- A. WALLGREN.
- » STURE SIWE.
- C. GYLLENSWÄRD.
- » P. PLUM.

Dr. C. FRIDERICHSEN.

- A. SUNDAL.
- V. RANTASALO.



Acute gastro-enteritis accompanied with toxicosis in infants.

By

S. SIWE.

The cases of acute gastro-enteritis with toxicosis recorded during the last ten years have been predominantly based on infection. In a series of 75 cases between 1 and 14 months of age all cases showed marked dullness to sopor, about 30 per cent were extremely restless, and 22 per cent suffered from convulsions. Almén was positive in one third of the cases, and Heller in 17 per cent. The blood sugar values varied between 0.09 and 0.23 with great fluctuations in the individual cases. The rest nitrogen was pathologically high in almost 60 per cent of the cases; pathological sediment was also often observed. Repeated lumbar punctures showed an increased amount of cells in about half the cases; raised protein values in the liquor were still more common (up to Bisgaard 1: 80). Sometimes these pathological findings were not made at the first lumbar puncture, but only later on.

While acidosis (assessed according to excretion of acid and reserve of alkali) does not amount to so high values that it can be considered to play more than a secondary rôle for the development of the pathological picture, exsiccosis and toxicosis are of main importance, and the treatment should therefore aim at influencing these factors by means of administration of fluids and of resorption-preventing agents (animal charcoal).

By applying treatment on these lines we have succeeded in reducing the mortality to 20 per cent.

STURE SIWE: Referat av föredrag vid kongressen.

2.

Nosocomial malignant Diarrhoea and Vomiting in Infancy.

By

ARNE NJÅ.

Malignant gastro-enteritis in infancy is among those diseases which showed a decided increase during the war. Also, in the Scandinavian countries, where for decades malignant diarrhoea and vomiting had presented no particular problem, several epidemics occurred. From Sweden the condition has been described by Selander 6, von Sydow 7 and Lichtenstein 3. In Denmark the subject was discussed by the Danish Pediatric Society in March, 1944 1. Since then, also, there have been epidemics of gastroenteritis in Denmark. Vald. Poulsen stated in a communication to Prof. Lichtenstein in November 1945 that since 1943, gastroenteritis of a more or less serious nature has apppeared in practically every Children's hospital and Children's Home in Copenhagen and its vicinity, about 50 epidemics in the course of two years with an average death-rate of 40—50 %. The majority of the cases were nosocomial.

In Finland there have also been many cases of malignant diarrhoea during the war ⁵, some of which probably belong to the same type as that described in Sweden and Denmark.

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In Norway, before the war, very few cases of gastroenteritis were treated in the children's ward of Rikshospitalet, only 3—9 per year. In 1941—43 came a decided increase in the number of patients, but the disease was relatively benign, and there was no nosocomial case

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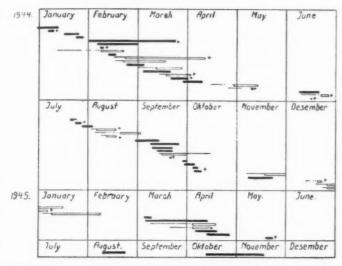


Fig. 1. A view over the duration of the hospitalization of the different patients. indicates patients admitted for gastro-enteritis. indicates patients with gastro-enteritis aquired in the hospital. indicates the period of hospitalization before the outbreak of gastro-

enteritis. indicates the time the patients spent in their homes before readmission for gastro-enteritis.

during these years. 1944, however, shows quite a different picture. Besides a further increase in the number of patients suffering from gastro-enteritis, we notice that the majority of them are under 1 year of age, while cases in older children dominated the casematerial in the preceeding years. 1944 also showed an increasing mortality in the disease, of which 17 cases ended in death. In children over one year we saw chiefly light cases, which have probably nothing to do which the actual disease. But one case, of a 14 months old girl, ending in death, had all the characteristics of malignant diarrhoea in infancy, and is counted among those cases. There were, therefore, 43 such cases in 1944. 26 of these can be classed as severe, 17 as fairly severe and light. In some of the latter cases it is difficult to distinguish between the actual disease

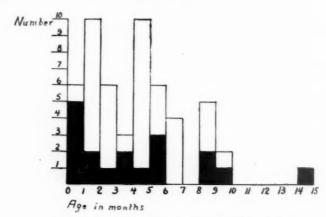


Fig. 2. Age grouping and mortality in the different ages.

and an acute dyspepsia. 27 of the 43 patients came to the hospital for gastroenteritis. Of these 9 died. 16 came to the ward for other aliments and acquired gastroenteritis during their stay there or developed symptoms of this disease immediately after their release and were readmitted. Of these, 8 died. Of the 27 admitted for gastroenteritis 16 represent nosocomial infection as they have been acquired in different infant's homes and maternity wards. Only 11 cases were contracted in the home. The cases were distributed over the whole year.

In 1945 continued occurrence of sporadic cases was observed, 10 cases in all, the majority of them in the first five months of the year. Three of the cases during those months were nosocomial, and none of them died. Since the end of the war we have not observed epidemic occurrence of malignant gastroenteritis though we can give no explanation of this fact.

We get an idea of the contagiousness of the disease from fig. 1, which gives a survey of the patients stay in the hospital. We notice that, as a rule, the nosocomial diarrhoea and vomiting arises in conjunction with other cases which are treated simultaneously in the ward. In April, 1944, the infant's ward was closed for a short while, which appeared to be effective. However, several cases

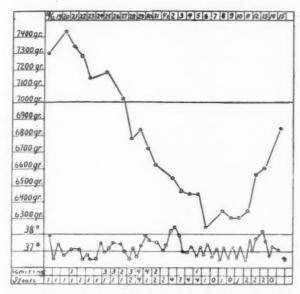


Fig. 3. 6 months old boy suffering from epilepsia.

occurred without any apparent connection with other diarrhoea patients. These observations indicate that there may be healthy carriers of infection among the patients or the nursing staff, or that unregistered, subclinical cases may spread the disease. Vald. Poulsen thinks that the disease is spread by air infection, and that children are infection carriers for several weeks after they are apparently cured. In some cases he has seen the disease transmitted by healthy children, and he believes that adults can also carry the infection.

In 1944 and 1945 we had 53 cases in all, with 18 deaths (34 %). There were rather more boys than girls, 30: 23. Lichtenstein's ³ records show the same relation. We have not been able to prove any difference in mortality between the two sexes, contrary to Lichtenstein who found a mortality of 42.9 % for boys and 19 % for girls.

Fig. 2 shows a survey over the age grouping and mortality

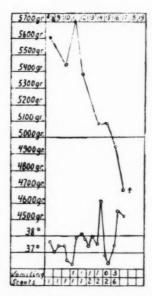


Fig. 4. 8 months old girl admitted for dystrophia.

in the different ages. We observe that the mortality is greatest in the youngest age group.

43 of the patients were bottle-fed at the time they developed the disease, 8 were partly breastfed, while only two were exclusively breast-fed. This much lower percentage of breast-fed, considering the total number of infant inmates, gives us the definite impression that naturel feeding produces a relative immunity against the disease.

Characteristic symptoms were vomiting, diarrhoea and intoxication with dehydration and loss of weight. In many cases the onset of the illness was insidious, with loss of appetite, casual gulping and vomiting, weight loss, and after some days diarrhoea and the typical signs of toxemia developed. In some instances the diarrhoea was severe, with numerous, watery, spouting stools, but in the most cases the diarrhoea was not prominent. Complete loss of appetite with gulping and vomiting was especially typical. Even

in cases with moderate or no diarrhoea, rapid exsiccation and loss of weight occurred. Figs. 3 and 4 show examples of this. The temperature showed no characteristic feature.

Diagnosis was difficult in many of the nosocomial cases as the patients were in a bad condition beforehand. Some had vomiting, some suffered from chronic dyspepsia and emaciation and two were treated for lues congenita. We notice that 7 of the nosocomial cases occurred in patients suffering from eczema.

Parenteral infections do not appear to be of importance in our data. In only 8 of the patients there were definite signs of parenteral infection, chiefly of the respiratory tract.

The treatment was the usual one with plenty of liquid per os, subcutaneous, intravenous and intratibial. Further the patients were given blood transfusions and stimulantia. In some of the later cases we gave repeated intravenous plasma infusions, up to 100 ml. This had a beneficial effect. Sulphathiazol and sulphaguanidine were administered in some patients, without convincing results. Lichtenstein 3 had the same experience. He has also tried penicillin with the same negative result. Henderson 2, on the contrary, found a considerable decrease in mortality from the epidemic diarrhoea in new-born after he began to give them sulphaguanidine, and he strongly advises the use of this medicament.

After one or two days fasting, we began a careful feeding, preferably with increasing portions of mother's milk.

Post mortem examinations have sometimes been quite negative, sometimes slight catarrhal changes in the intestinal mucous membrane were found. Nothing was found which can help to clear up the ethiology and pathogenesis of the disease.

The bacteriological investigations have given no basis for any definite ethiology. This is in accordance with the experiences from other countries. Several authors suggest the possibility of a virus infection. Many circumstances point in that direction: None of the known pathogenic microbes have been proved to be the cause of the disease. It is highly contagious, and its spread in the hospitals is not to be arrested by the hygienic precautions which for decades have been sufficient to prevent the spread of gastroenteritis. The disease has, to some extent, gone from bed to bed (Lichtenstein),

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but it is noteworthy that it has attacked the weakest, irrespective of their place in relation to the other patients. This indicates that we have to do with an air borne infection, in the same way as in other virus infections. The varying receptibility, therefore, may be thought to decide whom will be attacked. The consequence of these conditions is, that these patients for whom hospital care is necessary, should not be placed in ordinary children's wards but in epidemic wards where the strictest isolation can be maintained.

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3.

Pyuria in Finnish Children, 1933-1945.

By

PER FORSSELL.

»Pyuria» in childhood is not a pathogenetic unitary conception; the denomination was introduced by Kleinschmidt because — as he points out — it is not possible to differentiate between inflammation of the bladder, the ureter, or the pelvis in individual cases, particularly as regards infants and small children who are not able to describe their symptoms, whereas in older children and adults a localization of the inflammatory process may be made in many cases.

Pyuria is considered a fairly common disease in children, particularly in their first years. The frequency of the disease is calculated at 1 per cent of all policlinical and private practice cases; in regard to hospital material the double figure is mentioned (NOEGGERATH and NITSCHKE).

As there is an impression in Finland of the frequency of pyuria having decreased greatly in latter years, I have studied the case-histories at my disposal at the Children's Clinic in Helsingfors and at the Maria Hospital, for the period 1933—1945. The patients admitted into the first mentioned hospital were, practically without exception, children from the rural districts from all over the country, while the cases from the latter hospital comprised only children from the capital. As no differences in any respect between the children from the country districts and the town children were stated the groups of patients in this investigation were not separated.

^{3 -} Acta pædiatrica. Vol. XXXV.

The total number of pyuria cases during the above-mentioned period war 389; 71 (18.3 per cent) were boys and 318 (81.7 per cent) were girls. This division of sexes corresponds well with figures published at an earlier date (Noeggerath and Nitschke, Seidlmayer). The Table below gives the grouping of age and sex in my material:

Age					Moi	nths							Ye	ears		
A go	0-	-3	3-	-6	6-	_9	9-	-12	0-	-12	1-	-2	2-	-15	To	otal
Sex	ð	Q	3	Q.	3	ę	3	ę	3	ę	3	9	3	2	8	9
Number of cases	2	9	12	38	8	39	10	61	32	146	13	53	26	119	71	318

The Table shows that almost half the number (45.8 per cent) of all the cases were infants. About two-thirds of the patients (62.7 per cent) were less than two years of age. In all age groups the girls were four to five times more numerously represented than the boys.

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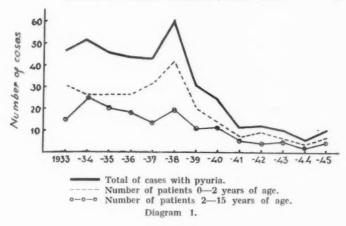
and

Up to the year 1939 the pyurias constituted 2—3 per cent of the total of all cases treated in the hospitals. From this year on a distinct decrease was observable; in 1940—45 0.2—0.4 per cent only of the total number of patients admitted to the hospitals suffered from pyuria. Diagram 1 has been worked out for the purpose of illustrating the diminution in the frequency of pyuria.

The diagram shows that the diminution in the number of pyuria patients was particularly marked in the age group 0-2 years.

The diagnosis chronic pyuria was made in seventeen cases. Only one of these was an infant while all the other patients were above two years of age. The distinctly stronger tendency of infantile pyuria to heal spontaneously in comparison with pyuria in older children has been stressed earlier by Rhonheimer and Unshelm among others.

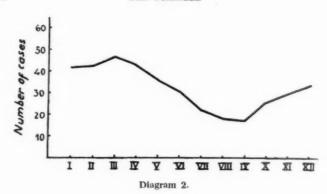
According to Sundal divergences of various scope in the structure and function of the urinary passages predisposes these organs highly to urinary infections of long duration in children. Unshelm



points out that when chronic pyurias arise acquired diseased changes in the neighbourhood of the urinary passages deserve greater notice in pediatrics than has been the case up to date. He assumed that in his series of investigations abdominal tuberculosis was, in three cases, a contributory factor to the chronicity of the infection in the urinary passages. In my material pyonephrosis was diagnosed in seven cases of which one patient was a girl of nine months. In one child a stone in the urinary tract was found and another child was afflicted with tuberculosis of the mesenteric glands. In the remaining ten patients with chronic pyuria no anatomical or functional abnormalities in the urinary tracts or in their vicinity were observed. There is a possibility of other cases having been discovered if all the chronical pyurias had been subjected to pyelographic examination.

The total mortality rate among my patients was 3.3 per cent. Unshelm mentions that an uncomplicated pyuria in older children, in opposition to that in infants, is not a deadly disease in an acute stage. Ten of the thirteen children in my material who had died were infants. The mortality among these was 5.6 per cent. This figure is decidedly less than the figures given by Block, Lasch and Dingmann, Seidlmayer (12—44 per cent).

GÖPPERT has observed a heavy increase in pyurias during the



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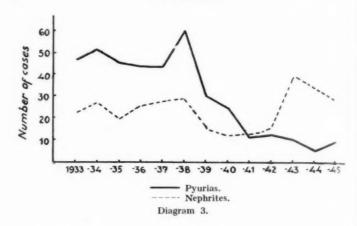
period May to August. This was not so in my series of investigations. Diagram 2 shows that the frequency of disease in my material reached a minimum in July-September while the majority of the cases occurred during the first months of the year, the season of infections belonging to the group of influenza. The association between pyuria and these diseases has been stressed earlier by Bessau, Finkelstein, Forbes, Armand-Delille and Bespaloff, Lasch and Dingmann.

In my data a coli-infection was observed in 95 per cent of the cases. In the remaining cases enterococci or staphylococci were observed in the urine. In one case of chronic pyuria with pyonephrosis streptococci were able to be cultivated. In solitary cases the urine contained numerous bacteria of coli type while pus cells were completely absent.

SEIDLMAYER (1940) and UNSHELM (1942) have stressed that prontosil possesses a decidedly more rapid therapeutic effect in pyuria than preparations used earlier (urotropine, salol, etc.). SEIDLMAYER, whose case-histories comprised pyuria in girls only, arrived at the result that with prontosil medication the urine in infants was free from pathologic elements on an average on the seventh day of treatment; corresponding figures for children of nursery age were 5.9 days, and for school-children 4.0 days. Unshelm stated a complete cure on an average within a fortnight in children from 1—13 years of age.

For the purpose of comparing the influence of different therapeutics on the time required for cure I have calculated the time in the acute, uncomplicated pyurias in my case-histories. I have considered the time of cure as lasting until the patients were free from fever, the general condition satisfactory, and the urine contained neither albumen, white blood corpuscles, nor bacteria. Older preparations (urotropine, salol, etc.) were used for treatment of pyurias up to May-June 1936 (85 cases); from this date to September—October 1939 the patients were treated with prontosil (75 cases), and from then on with sulpha preparations (42 cases The time of cure was, as regards children belonging to the first period, on an average 23 days (for infants 26 days, for older children 22 days). Prontosil brought about a cure on an average in 19.5 days (infants 21 days, older children 17.7 days), and sulpha preparations on an average in 12 days (infants 11 days, older children 13 days). The investigation thus reveals that no reduction in the time of cure was obtained with any certainty with prontosil medication in comparrison to earlier preparations (urotropine, salol, etc.) but it seems, however, as if the sulpha preparations would have brought about a decidedly more rapid recovery.

Discussion. The coincidence between the greatly decreasing frequency of pyuria which has been observed even in private practice and in policlinical cases, and the introduction of sulpha preparations in treatment of acute infections is remarkable. At least in Finland the sulpha preparations have been used largely both with and without the physician's prescription in febrile diseases of various kinds. Certain sulpha preparations can still be bought freely at the chemist's while again physicians' prescriptions are required for certain other kinds. It is thus easy to assume that sulpha treatment of the »primary disease» has led to the elimination of the infectious matter or to it having become weakened to the extent that the pyurias, as complications, have become more uncommon than before. For the same reason the attacks of pyuria of latter years have probably not been of the same gravity, i.e. strongly affected general condition, signs of intoxication, meningeal irritation symptoms, etc., which were often characteristic, particularly of infantile pyuria, during former years.



An incident deserving special attention in this connection is the fact that although the frequency of pyuria is greatly reduced the nephrites in the same casematerial do not show a tendency to decrease (as seen from Diagram 3). The diffuse glomerulonephrites do not arise, as is the case with pyurias, in immediate connection with the primary disease; not until after a certain time of incubation (allergia?) do they appear. As is known, no special effects of sulpha preparations are observed in nephrites either in adults or in children. This may also explain the conception of the lessening frequency of pyuria being due to the introduction of sulpha preparations in treatment of acute infections. Another possibility might be that the decrease is connected with a lesser affinity to the kidneys, during the latter years, in influenza and other infections (a changed genius epidemicus) which is partly contradicted by the fact that the nephrites have not decreased in number, as has been mentioned.

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4.

Treatment of Pneumonia with Shock Doses of Sulfathiazol in 688 Cases.

By

KNUD WILKEN-JENSEN.

After Platt in 1940 had reported the results of his treatment of pneumonic children with one dose of sulfapyridine C. Friderichsen in the children's department of Sundby Hospital (Copenhagen) on the 1st of February 1941 began to treat pneumonia and capillary bronchitis with sulfathiazol in shock dosage. In the beginning the sulfathiazol was administered in a single dose only, but since the spring of 1942 severer cases were treated with two or more shocks according to the patient's condition. One shock continues to be the routine treatment however. Up to the present shock treatment has been applied in 638 cases of pneumonia and in 50 cases of capillary bronchitis.

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Pneumonia.

As is evident from Table I, 514 children with pneumonia have received one shock, 81 children received 2 shock doses, whereas 43 children have received 3 or more shocks. The distribution of the material appears from the Table.

The first columns tell their own story. The condition of the patient is recorded as I, II or III, I meaning very debile (some of the patients being moribund on admission), II, rather debile and, III, lighter cases, respectively. The respective figure refers to the patient's condition at the moment the first shock was administered, but it does not always correspond to the extent and

Table I.
638 cases of pneumonia

Age	Number	Broncho- pneumonia	Pneumonia crouposa	Uncertain	Co	ndit	ion	shock	shocks	or more	Pneumo- cocci
A.	Nu	Bro	Pneu	Une	I	11	111	1 s	21	3 or sh	Pne
0-1	179	153	4	22	63	58	58	139	24	16	105=59 %
1-2	137	111	10	16	32	51	54	106	19	12	98=711/2%
2-11	322	200	102	20	76	108	138	269	38	15	236=73 %
0-11	638	464	116	58	171	217	250	514	81	43	439=69 %

gravity of the pneumonia. A shock dose amounts to 30 cg of sulfathiazol per kg body-weight, the maximum being 4 g. It is administered perorally, stirred up in a little fluid, mostly warm milk, with the help of a spoon. Afterwards the child receives a little water to rinse its mouth; later, however, it is not allowed to drink anything or, at the most, a teaspoonful of water now and then. In that way a high sulfathiazol concentration in the blood is attained. After the lapse of four hours the patient is allowed to drink plenty of water in order to wash out the sulfathiazol. In isolated cases only the shock dose was administered by intramuscular injection, cibazol, sulfathiazol or sulfamethyl-thiodiazol (lucosil) being used in those cases. A difference in the effect of these two forms of treatment was not observed, but as the injection of sulfathiazol in one case gave rise to necrosis, injections were resorted to as little as possible. It may happen that a patient suffers from vomiting soon after peroral administration of sulfathiazol, and in such a case the shock is repeated and recorded as one shock. In most cases, however, the child readily becomes calm or goes to sleep without requiring any sedative, which have, therefore, been given very seldom.

The children who have received two shock doses generally received the second 48 hours after the first. The shortest interval between two shocks was 4 hours (for a patient who died), whereas the longest interval was six days. Similar intervals hold for the patients who received three or more shocks. In order to obtain an

easy survey, however, the same group comprises those who during their hospital stay developed a new pneumonia, whence the intervals became longer.

Pneumococci.

Pneumococci were demonstrated in 439 patients (69 per cent) after pharyngeal swab. All the surviving patients were examined on three successive days. I draw attention to this fact, because in 139 patients pneumococci were demonstrated from a single swab only (in 32 per cent of the pneumococco-positive cases). This is not due to the disappearance of the pneumococci immediately after the commencement of treatment, for we have made the same experience as was made in other quarters that the type may be found again several days after the temperature has returned to normal.

Secondary effects.

Of secondary effects of the treatment (see Table II) vomiting and rises of temperature are the most frequent, the latter attaining fairly high degrees without, however, affecting the patients. Vomiting rarely is recorded more than once for each of the patients mentioned. As secondary effects should be mentioned 18 cases of exanthema + 3 dubious cases, 19 cases of microscopic hematuria, one case of leukopenia, and one case of medicamental agranulocytosis. All the cases were transitory, requiring no treatment.

Table II.

Age	Vomitings	Second. rise of temp.	Otit. med. supp.	New pneumonia	Mors	Exanthema 18 (+3?) Hematuria (micr.) 19 Leukopenia 1 $\begin{cases} 6000 \text{ WBC} \\ 720 \text{ Leukocytes} \end{cases}$
0-1	39	42	59	9	17	Agranulocytosis 1 2000 WBC 380 Leukocytes
1-2	38	44	36	8	3	
2-11	75	94	35	9	1	Pleuritis serosa 19 Pleuritis purulenta 4
0-11	152	180	130	26	21	Meningitis serosa 6

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Complications.

The most frequent complication was otitis media of which there were 130 suppurative cases. Moreover there were 19 cases of serous pleurisy, 6 cases of serous meningitis. In 4 cases purulent pleurisy developed so that the patients had to be transferred to the surgical department.

Mortality.

Twenty-one (3.3 per cent) of the 638 children died. This number will be accounted for in detail. Ten of the 21 children had congenital affections, three of them presenting morbus cordis congenita, five were premature, debile children, one of whom even had a pulmonary abscess, and two children were mongolian idiots. The three children with morbus cordis died within 24 hours after admission, and two of the five debile children died 6 and 9 hours respectively after admission, one of them died 28 hours after admission, another died on the 4th day, and the child with the pulmonary abscess died on the 6th day. The mongolian patients died 13 and 16 hours respectively after admission. One of the remaining eleven children was one day old and had aspiration pneumonia; it died after 38 hours. One child who had tetanus neonatorum survived 4 days. One child with purulent meningococcus meningitis died barely 22 hours after admission. One 2 monthold child with malign gastro-enteritis died within the first 24 hours. Two atelectatic children died 12 hours and 13 days respectively after admission. One child with sepsis died after barely 48 hours. The last four children were admitted in moribund condition and died less than 6 hours later.

Deducting the children who died within 24 hours after admission, there are left 7 cases of death, i.e. a mortality of 1.1 per cent. Again deducting from these seven cases the three patients with congenital affections (two with a.t.n. and congenital debility and one with a.t.n. complicated with lung abscess), and one patient with tetanus, there are three deaths left, namely, the three underlined cases recorded on Table III. That means to say that the lethality amounts to 0.47 per cent.

Table III.
Fatal cases

Complication	Num- ber	Age	Time after admission h=hours d=days
A.T.N., Debil. cong.	5	2/52-3/52-4/52-2/12-4/12	28 h- 6 d- 9 h- 4 d-6
Atelectases pulmon.	2	2/12-11/12	13 d— 12 h
Gastroent. ac. malign.	1	11/365	24 h
Meningitis (meningococ.)	1	3/12	22 h
Mongolismus	2	1-2	13 h- 16 h
Morbus cordis congen.	3	6/52-1 3/12-1 5/12	8 h- 6 h-24 h
Moribundus	4	3/12-4/12-4/12-8/12	4 h- 6 h- 6 h- 6 h-
Pneumonia ex aspirat.	1	1/365	38 h
Sepsis	1	9/12	48 h
Tetanus neonatorum	1	1/52	4 d

Treatment with one shock.

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On Table IV are recorded the figures indicating how soon after treatment the temperature, the respiration and the pulse rate drop. The temperature is measured, respiration and pulse rate are counted until the temperature has dropped below 38°. Afterwards that is generally done only in the morning and evening, unless the patient's condition is unsatisfactory. Therefore the figures—particularly those recorded for the pulse rate—are not very precise, although they clearly show in what order the functions of the organism approach normal. Finally the days of illness are recorded for the complicated and the uncomplicated cases as well as the average.

These figures are fairly high, even considering that the high average figures are due to the many different severer or lighter affections which were found during the children's stay in hospital. On reviewing the case-histories, however, it is seen that the days of illness for the uncomplicated cases have increased during the war, and this may for obvious reasons be attributed to a circumstance which frequently occurred, namely, that it was difficult to discharge the children on account of the lack of kindergartens and crèches where they could be looked after, while the parents

Table IV.
514 cases treated with one shock

Age	Fall of temperat. hours	Fall of respir. hours	Fall of pulse days	Days without complic.	Days complic. or other diseas.	Days average
0-1	141/2	37	4	18.3	29.3	25
1-2	141/4	25	3	15.6	31.1	23.4
2-11	12 1/3	18	2	16.1	24	19.5
-11	13 1/2	24	3	16.5	27.3	21.8

went to work. In some cases the parents certainly also have desired that the child, on discharge, should have regained so much strength that, in case of air-alarm or eventual evacuation, it would be able to resist chill and fatigue.

The whole of Table IV applies only to those patients who have received one shock. Therefore the average number of days of illness is actually somewhat lower than that recorded for the total case-material — even though the difference is slight — for naturally only the severer cases have generally required more than one shock.

Discussion.

If the result of the shock treatment is to be accounted for, it is difficult to find cases of patients suitable for comparison. In deference to Dr. Hesselman I shall be content with mentioning the Danish data which might be taken into consideration as basis of comparison, although I am bound to state at once that I have not been able to find any really suitable and sufficiently comprehensive material published in Denmark the greatest works originating from isolation hospitals. Apart from Friderichsen & Søbye's work comprising 59 cases of pneumonia treated with continuous dosage of sulfathiazol and with a deathrate of 0, only one casematerial of 50 has been reported from a non-epidemic ward, namely, by Vermehren & Vermehren who treated the patients with continuous peroral administration of alphasol, likewise without any deaths. These data comprise fewer children, however, so that they

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are not suitable for comparison. From Marselisborg Hospital in Aarhus two reports have been published, one, by Heintzelmann, comprising 74 children who were treated with sulfapyridine and of whom 12 died, the other, by Nielsen & Nørby, comprising 137 children who received sulfathiazol treatment and of whom 5 died. From Blegdamshospital in Copenhagen Roelsen has described 140 sulfathiazol-treated children with pneumonia, nine of whom died. From the section for epidemic diseases of Frederiksberg Hospital Nissen and co-workers have reported 323 cases altogether, treated with sulfapyridine, sulfamethyl-thiazol, sulfathiazol, lucosil and alphasol, eventually combined, and combined with serum, with twenty deaths. Thus the mortality rate for Aarhus is: 16 and 3.65 per cent, Blegdamshospital: 6.43, and Frederiksberg: 6.2 per cent, and if all the published cases treated with continuous chemotherapy — also including the two reports without lethal cases the mortality rate amounts to 5.87 per cent. In the face of this stands the total mortality of 3.3 per cent of the present casematerial. On examining the previous data in order to deduct those patients who died within 24 hours or of other causes than pneumonia — as far as possible according to the reports — I arrive at the following numbers: Heintzelmann 6 instead of 12, Nielsen & Nørby 2 instead of 5, Roelsen 4 instead of 9, Nissen and coworkers 7 instead of 20, which gives a reduced mortality of 2.4 per cent altogether (19 deaths to 783 cases). To this figure corresponds the mortality rate of 0.5 per cent in the children's department of Sundby Hospital for the cases treated with shock. As to mortality the shock therapy thus seems to have the lead, even if regard be paid to the disparity of the cases.

Another essential advantage is the circumstance that the patient has to take 'medicine' once only. That is a great relief for the nurses, for it means that the patient gets rest, which can scarcely be overrated; nor do nausea and vomitings recur every fourth hour or, if they do occur, they are rapidly recovered from. Therefore the shock therapy is far easier to carry through in the patient's home, where the physician himself eventually can give the child the 'shock' and the mother take charge of it afterwards unaided

by a trained nurse.

Table V.
50 cases of bronchitis capillaris.

	Num-	Bronch.			ion		2	3 or	Vomi-	Otit.		ors
Age	ber	capill. spast.	I	11	m	shock	shocks	more shocks	tings	media supp.	< 24 hours	> 24 hours
-1	43	12	22	15	6	12	21	10	13	9	5	2
_2	5			4	1	1	1	3	1	4		
-3	2		1	1		1	1				1	
-3	50	12	23	20	7	14	23	13	14	13	6	2

Finally, the total shock dosage only amounts to about half the quantity of the remedy required for continuous treatment, which again implies a reduction of expenses.

Capillary bronchitis.

During the 5 years from January 1st 1941 to December 31st 1945, fifty cases of capillary bronchitis, twelve of which were of the severest type: spastic capillary bronchitis, have been treated in the same department of Sundby Hospital. Eight (16 per cent) of those patients died. Six of these eight children died 2, 6, 8, 13, 15, and 20 hours respectively after admission; among these were two cases of the spastic type, two patients with atelectases, and two with emphysema, one of whom was 2 years old. The diagnosis was verified by autopsy. One of the two patients who survived for more than 24 hours, a 6 week-old atrophic child weighing 2.8 kg, suffered from malign gastro-enteritis. Thus there is only one case left in which the shock therapy may be said to have failed.

The composition of the material is evident from Table V. The treatment consisted of sulfathiazol shock which, in isolated cases, was given as intramuscular injection. As is seen, the majority of the patients received more than one shock and, besides, strong, stimulating treatment with oxedrin, lobeline, adrenalin (in one case successfully administered intracardially), and oxygen. In order to facilitate expectoration, vapour, ephedrine and ipecacuanha were given. As sedatives were used bromisoval, codeine and phenemal.

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Against spasms was given chloral, against hyperpyrexia, acetyl-salicylic acid. Finally there were a few patients who received saline infusion or transfusion of blood.

The motive of applying shock dosage with sulfathiazol as treatment of capillary bronchitis is the same as in pneumonia.

Conclusion.

The result of the making up of the material confirms the advantages of shock treatment pointed out by Friderichsen & Søbye in 1941. These advantages shall here be counted up in a slightly extended form:

1: It is easier to give one shock dose, eventually repeat it on one of the next days, than to give a dose every 4 hours.

2: The children get more rest, they are not alarmed when the nurse comes, their sleep is not disturbed.

3: There is less nausea and vomiting.

4: It saves time in the ward, and the risk of mistakes is reduced.

5: The results are equivalent to or, perhaps, even better than, the results of continuous treatment.

6: Shock treatment is cheaper than continuous treatment.

7: It is easy to administer in practice, if the physician is conversant with it and eventually can give the child the tablets himself.

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5.

Massive Single-Dose Chemotherapy in Pneumonia in Children.

By

B. H. HESSELMAN.

An account is given of 195 cases of pneumonia and bronchopenumonia in children from 0—15 years of age, treated in the medical wards of Kronprinsessan Lovisas Barnsjukhus during the period 1. 3. 1941—1. 7. 1945.

In all the cases chemotherapy has been given in the form of a single massive dose. In 48 cases (24 %) the massive dose treatment has been supplemented by continuous chemotherapy. Sulphapyridin, sulphathiazol and sulfadimin have been used. The dosage has been 0.3 g per kg body weight for children under 3 years, and 0.2 g per kg body weight for the others, with 8 g as the maximal dose.

There have been few complications, and the toxic side-effects have been extremely slight. 5.6 % fatal cases are recorded, but if those cases are subtracted, where pneumonia has appeared as a complication of a serious congenital malformation, the mortality is 2.1 %.

As the massive single-dose treatment is technically easy to carry out, gives the patients more rest than does the continuous treatment during the period when the illnes is most severe, lessons to a considerable degree the work of the hospital personnel, gives a result which can be favourably compared with that of continuous chemotherapy and gives rise to few complications, this treatment can be recommended for pneumonia in children.

Good results have also been obtained with massive singledose treatment in cases of capillary bronchitis.

4 - Acta pædiatrica. Vol. XXXV.

Discussion on Papers 1-3.

LICHTENSTEIN: In Stockholm, as elsewhere in Scandinavia and in other parts of the world, the appearance of an infectious form of acute dyspepsia has been observed in recent years — also nosocomially. In describing these cases one is faced with the great difficulty of separating them from acute cases of dyspepsia of the ordinary, common type. To guard against any of the latter being included, none but cases of the choleriform type, characterized by more or less acute attacks of violent vomiting, serious diarrhoea, considerable loss of weight, obvious signs of exsiccation and a lowering of the general condition are being dealt with in the present report. At Crown Princess Lovisa's Children's Hospital 61 such cases were treated in 1945. Of these, 14 had contracted the illness at home, 3 in some other hospital and no less than 38 in the Children's Hospital itself and 6 within 1—4 days of their discharge. Thus, of 61

Cholera Infantum in the General Children's Hospital. 1860—86 (from Hofsten's paper 1887).

During this time were treated 11,800 infants 3,300 (=27.9 %). of whom died,

Year	Number of	children	Total	Year	Number of	children	Total
2 0443	Healthy	Dead		100.	Healthy	Dead	1011
1860	6	16	22	1874	9	26	35
1861	13	25	38	1875	13	68	81
1862	9	15	24	1876	12	50	62
1863	11	17	28	1877	12	42	54
1864	11	26	37	1878	4	19	23
1865	5	34	39	1879	12	16	28
1866	3	11	14	1880	7	13	20
1867	-	4	4	1881	5	12	17
1868	5	15	20	1882	3	16	19
1869	3	11	14	1883	3	10	13
1870	1	28	29	1884	11	16	27
1871	10	36	46	1885	21	40	61
1872	14	46	60	1886	44	58	102
1873	17	64	81		-	-	-
				Total:	264	734	998

The mortality rate in Cholera Infantum during the whole period — 73.5 % per cent.

17/9 cali + entero- cacci 29/0		coli + enleracossi	ijoo	100				Ħ	10
coli	18	5/9 17 2	9/9 16 3	3/9 15	14	13	12	-	
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					-			8	9

8		10	11	12	13	
	- Pa	19/4	18/4		1	16
7			+ pro	teus	,	15
	19/4				1	14
6	coli					
	-	14	13	12	11	

cases 41 were nosocomial. The illness was not of a seasonal character. The boys somewhat outnumbered the girls. 14 of the patients were breastfed, 15 partly bottle-, partly breast-fed and 32 exclusively bottle-fed.

With regard to symptomatology, a characteristic feature was a more sub-acute sickening than is usually observed in cases of cholera infantum. Vomiting has dominated, in many cases precluding feeding per os, often for several days. Diarrhoea stools have been loose, sometimes to the point of wateriness, sometimes mingled with phlegm, but never with blood. Albuminuria and cylindruria appeared in the majority of the cases. Relapses often occurred.

The most striking feature of these cases was their obvious and unmistakable infectiousness. It was repeatedly observed that the illness passed from bed, to bed just like a specific infectious disease, which is illustrated by the following diagrams:

This most remarkable characteristic is strongly suggestive of the cholera infantum of days gone by as described for instance by von Hofsten in his excellent treatise »Cholera Infantum in the General Children's Hospital of Stockholm in 1887». Some data from this work appear in the following table.

Obviously we are again, in several instances, up against an infectious and probably specific form of intestinal infection of a type that has not been observed in our country for several decades.

The causal agent is unknown, possibly a virus. The Americans Light and Hodes of the Johns Hopkins Hospital announced in 1943 that they had succeeded in isolating from cases of infectious dyspepsia, during four different epidemics, a filterable agent which invariably caused diarrhoea in calves and was untraceable in healthy children and calves. Of the cases under review only bacteriological tests were made which merely elicited the presence of un-specific intestinal bacteria, predominantly coli and, in a considerably lesser degree, enterococci and proteus.

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The mortality rate was high - 29.5 %.

An essential feature of the therapy is careful attention to the water-, albumen- and salt-balance.

Sulphate preparations and penicillin have had no noticeable effect in our cases.

Compulsory notification of cases of infectious acute dyspepsia in infants is now being enforced in Sweden until further notice.

C. FRIDERICHSEN: Prof. SIWE held that the importance attached to acidosis was exaggerated. Acidosis cannot be determined from the secretion in the urine but rather by examining the alkali reserve in the blood. A therapy directly focused on this we hold to be very important and conclusive as a life-saving factor. Acidosis occurs simultaneously with loss of weight, often before diarrhoea has set in.

Acidosis and loss of weight are characteristic symptoms in the first stages of malignant gastro-enteritis.

This illness, which with us always started in the maternity wards, has an incubation period of six days. Children attacked by this disease very often die of atrophy as late as four weeks after the appearance of the first symptoms of gastroenteritis.

SIWE: The alkali reserve in the blood has naturally also been examined as a matter of course. As no particular decrease was noticed, I formed the opinion that the effect of acidosis was less significant than had been earlier assumed. Absence of kidney lesions seems to be indicated by the slight increase in Rest-N, quickly receding albuminuria and rapid disappearance of sediments of a pathological nature.

RAIHA: Demonstrated a table compiled by Dr. Helve illustrating the frequency of nosocomial infections in the infants' ward (25 beds) of the Children's Clinic at Helsingfors.

The department was 100 % overcrowded. Mortality from nosocomial diarrhea 16.2 %,

» infections of the air-passages 2.9 %.

The symptoms were identical with those described by $NJ\lambda s$. Sulphatiazol and penicillin proved ineffective.

GJönur (Copenhagen): In Copenhagen we have had epidemics of much the same nature as those observed in Oslo and Stockholm. The illness progressed in the main as has already been described.

The epidemiological picture diverges on one point from that of Oslo and Stockholm. As far as I know, there has been no instance in Copenhagen of the illness occurring outside of hospitals, children's and maternity homes or in connection with cases discharged from infected wards.

There is one question which has given us much food for thought, namely the isolation of children who have been exposed to infection. We consider that the contagiousness is the same as in morbilli. Several maternity wards have been infected and there has been no possibility of closing them. In the beginning infected infants and those having been exposed to infection were isolated individually in wards for older children, but comparatively few cases could be dealt with in that way. Later, a special ward was established for all infected children, and a quarantine department in the hospital for epidemic diseases for children who had been exposed to infection. The latter, comprising 30 beds, proved insufficient, however, as a single case of the disease necessitates the closing of entire wards for a considerable period. The contagiousness seems to have declined lately,

but the problem of isolating effectively both infected children and those having been exposed to infection is still unsolved, and I should be interested to learn whether experiences elsewhere have been better than mine.

RANTASALO: The attached statistical table shows that the frequency of Pyelitis at the Hospital for Infectious Diseases in Helsinki has been very low, at least from 1937 onwards. The three deaths were all due to some other co-existent illness.

6.

The Breast Feeding of Mature Infants during the Neonatal Period, and the Influence of Some Factors on the Same.

By

JUSTUS STRÖM.

As is well known, the loss of weight in newly born infants is a perfectly normal condition. When the active breast milk secretion has been established after 3—4 days, the infants soon gain in weight again.

There is no doubt, however, that the infant's loss of weight often causes anxiety to the person taking care of it. For this reason, it is very common that breast milk from another mother, or not infrequently cow's milk mixtures, are added already in the maternity hospital. In this manner one tries to prevent the loss of weight, but one also hears that this is sometimes considered insufficient, and that one aims at reaching the birth weight already before the infant leaves the hospital. The existing tables of the calculated needs of breast milk during the first days of life, have undoubtedly also contributed to the fact that one endeavours to supplement the eventual lack with some addition.

Even though this conception of the nutritional problems of infancy is understandable, it is nevertheless not justifiable from the pediatric viewpoint. It cannot be unimportant if the infant is given additional food, and especially not if this is given by bottle as is the usual procedure. The infants suckle less effectively because of diminished hunger, and of the fact that the food is thus

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given to them in a simpler way, than the one generally offered by nature.

For this reason it seems to me to be of value to present the results of the nutritional regime, that I have practised for a period of 5 years as consulting pediatrician, firstly to the »Karolinska Sjukhuset», and later on the maternity hospital »Pro Patria». In this connection I have endeavoured to analyse some of the factors which are of importance to the nursing. ¹

Feeding schedule.

This investigation only comprises infants weighing more than 2,500 g at birth. Special methods are used in cases of premature children, which will not be given here. These infants are generally sent to special pediatric departments. This should be done at any rate with children weighing less than 2,200 g at birth. Between 2,200 and 2,500 g the same rules can usually be applied as to those weighing 2,500—2,700 g. This only means that the children are given 6 meals from the beginning. For children weighing more than 2,700 g at birth I have prescribed 5 meals. If needed, a change to 6 meals has thereafter been prescribed, as well as a change to the use of both breasts at each feeding.

Addition of breast milk or cow's milk mixture has not been permitted, except by doctor's prescription. It is preferable never to use cow's milk mixture at all. Only very exceptionally a situation arises necessitating the administration of anything but breast milk in a maternity hospital. If the stay in the hospital is not too short, there are nearly always some mothers, who, during the last days of their stay have an abundant milk supply, thus enabling one to cope with the situation. The maternity hospital should even be able to serve as a provider of breast milk to breast milk centres on the presumption that the usual hospitalization period reaches some ten days, as is the case in Pro Patria. Thus this maternity hospital delivered about 60 liters of breast milk to the centre during 1944. We were only compelled to apply for some breast milk on one or two occasions, for one or two days.

Addition of fluid in the form of ordinary water, however, has been made according to the following rules. 1. 10 % loss of weight or more. 2. Conditions with fever in the infant. 3. Outstanding dryness (tongue, lips), restlessness and screaming. 4. Birth weight of 4,000 or more. The quantities have been calculated so that the amount of breast milk \pm water in the second day has reached the amount of 30 g \times 5, with an augmentation of 10 g each meal pro die.

¹ I wish to extend my deep appreciation to professor Gunnar Dahlberg, Uppsala, for his scrutiny of my statistics.

Control of the amount of breast milk.

In order to be able to follow the feeding of the infants one should not be satisfied with noting their weight daily or every other day, as is so often done. Every meal should be weighed. This may seem an unnecessarily stringent rule, which would only add to the work of an already overworked staff, but, the time saved by reducing the extra feeding of the infants to a minimum, is considerable. Thus I have had no complaints from the staff once the weighing became part of the routine. On the other hand, after some time it was declared that a considerably increased sense of security and confidence was achieved concerning the estimation of the nutrition of the infant, a fact that was considered a great advantage. These mensurations of the breast milk quantities, undoubtedly contribute to a much more exact estimation of the additions necessary when leaving the hospital.

Case-material.

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The case-material comprises all living infants with a birth weight above 2,500 g born in »Pro Patria» during 1944, excepting multiple births, two infants whose mothers were so seriously ill (tbc and organic heart disease), that nursing could not be allowed, two more infants who were sent to pediatric hospital on the third day, and finally 9 infants who were ill. The infants have been divided into groups of ½ kg according to their birth weights.

As is shown by table 1 the total sum of the infants was 1074. Most of them fall into the groups 3,001—3,500, and 3,501—4,000.

Table 1.

Weight groups	Number	Primip	arae	Multip	arae	Mothers fants he	
		Number	%	Number	%	Number	%
2,501—3,000	109	68	62.4	41	37.6	64	58.7
3,001-3,500	387	196	50.6	191	49.4	235	60.7
3,501-4,000	371	157	42.3	214	57.7	210	56.6
4,001-4,500	168	42	25.0	126	75.0	86	51.2
4,5015,000	29	6	20.7	23	79.3	12	41.4
5,001-5,500	10	2	-	8		5	-
	1074	471	43.9	603	56.1	612	57.0

Table 2.

	Loss of	f weight	Day of	Su	pplei	ment	Suppl.
Weight group	Gm.	%	minimum weight	Num- ber	%	average number of days	the last day
2,501—3,000	222± 6.9	7.6±0.25	4.7±0.14	24	21.8	6.0	12
3,001-3,500	278± 4.4	8.2±0.13	4.9 ± 0.09	48	12.2	3.4	13
3 501-4,000	304 ± 5.0	8.4±0.13	5.2 ± 0.10	29	7.7	4.2	14
4,001-4,500	365 ± 7.3	8.4±0.17	5.7 ± 0.18	21	12.5	4.0	8
4,501-5,000	449 ± 19.0	8.3 ± 0.40	5.7±0.43	3	10.3	5.0	1
5,001-5,500	$524(\pm 32.6)$	$10.2(\pm 0.67)$	$7.2(\pm 0.66)$	3	_	1.3	1

The primiparae constituted 43.9 % and the multiparae 56.1 %. Here I must point out that I have not used the designation primipara in its obstetric sense, but I have regarded the mother from the pediatric viewpoint, thus considering her a primipara if she has not nursed an infant before. From the viewpoint of this investigation, it would be erroneous to consider all those women multiparous who have had an abortion earlier. From the table it is evident that the primiparae are mostly found within the low weight groups of the infants. 1

In the last column the number of cases where both mother and child were perfectly healthy has been recorded. This record has been made very strictly, so that e.g. mothers with anemia (<70% according to Sahli's method), have not been considered healthy.

The feeding can be judged in two different ways. Usually we primarily consider the result of the feeding, that is the infant's weight conditions, but we can also consider the amount of breast milk produced. The former method, however, has a difficulty to

¹⁾ Here I wish to point out that in the comparisons made between the primi- and multiparae, one should actually compare the same women when they had their first baby and when they had their subsequent ones. One may consider the possibility of a selection thus, that the women who have had several children are more suitable for the purpose, and that they for this reason also have more milk. It is, however, not likely that this mechanism of selection has any effect worth mentioning, and an attempt to consider it would incur great practical difficulties.

cope with in this respect, because of the additions it has been necessary to administer for some reason or other.

Before I proceed to analyse the influence of the separate factors further, I wish to present the results of my feeding method within the different weight groups in a table. Table 2 shows the maximum, absolute and relative weight losses within the groups. As to the differences between the procentual weight losses within the groups, the one between the groups 2,501—3,000, and 3,501—4,000 is statistically probable (0.8 \pm 0.28 %, i.e. more than 2.5 times the standard error). Concerning the time of the least weight, the difference is statistically established between the groups 3,001—3,500, and 4,001—4,500 (0.8 \pm 0.20 days).

The lesser weight loss in the lowest weight group, is probably due to the fact that a relatively greater amount of infants have been given additional breast milk, and that the infants between 2,501 and 2,700 g have been fed 6 times daily instead of 5. Concerning the infants in the weight groups 4,001—5,000 g which have their weight minimum later, one may perhaps assume that the administration of additional liquids has prevented an otherwise greater weight loss. The greater weight loss in the heaviest group suggests this, but the case-material is too small to draw a definite conclusion in this respect. On the whole the infants have at a maximum lost a mean of 8 % of their birth weights, by the employment of this feeding method. A certain but very slight tendency towards increased weight loss, and a later occurrence of the minimum weight has been established in the heavy weight classes.

As is known, many factors exert an influence on nursing, and it has been my purpose to attempt an analysis of some of the most important during the neonatal period. First of all it can naturally be established that illness has a deleterious effect on nursing. To this I will return presently.

In normal conditions, i.e. when both mother and child are healthy, experience suggests that some factors must be considered of major importance. One of these factors in the mother, is whether she is primi- or multiparous. Another factor in the mother is her age. One has also reasons to assume however, that the degree of development of the infant is of certain importance. One knows that the

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Table 3.

	Numb.	Average Numb. age of the	Average weight of the	Largest loss of weight	Day of minimum	Loss of weight on the	Infants with supplement	with	Average number of days	Infants with supple-
*		mothers	birth	in per-	weight	-	Numb.	%	supple- ment	ment the last day
Primiparae										
Healthy	231	27.3±0.3	$3,426\pm\ 27.0$	8.4±0.17	5.2 ±0.13	5.6 ± 0.23	27	11.7	3.5	9
Anaemia	84	27.9±0.1	$3,501\pm52.9$	8.7±0.30	5.0±0.19	6.3 ± 0.37	11	13.1	4.5	4
Albuminuria	39	27.5 ± 0.9	$3,341\pm 72.0$	8.3 ± 0.47	4.7 ± 0.23	5.6 ± 0.53	6	23.1	5.0	3
Resorption fever	44	28.6 ± 0.7	$3,558\pm52.8$	9.1 ± 0.38	5.3 ± 0.27	6.9 ± 0.47	00	18.2	5.5	4
Other diseases	57	28.6±0.7	$3,593\pm62.3$	8.9 ± 0.32	5.2 ± 0.23	6.2 ± 0.44	14	24.6	4.9	6
Healthy delivered with										
forceps	16	31.7 ± 1.6	$3,376\pm128.8$	9.3 ± 0.81	5.0 ± 0.43	6.2 ± 1.06	60	18.8	4.3	-
Multiparae										
Healthy	382	32.9 ± 0.3	3,636 ±	24.6 7.9±0.12	5.2 ± 0.11	5.5±0.16	26	8.9	33.00	12
Anaemia	134	32.8 ± 0.4	3,803士 41.5	8.3±0.22	4.9±0.18	5.9 ± 0.30	6	6.7	3.6	3
Albuminuria	35	33.2±0.8	3,765 + 84.5	8.2 ± 0.37	5.2 ± 0.35	5.8 ± 0.53	2	5.7	5.5	2
Resorption fever	10	34.5±1.1	$3,601\pm123.4$	9.0 ± 0.76	5.2 ± 0.65	7.8 ± 0.98	1	10.0	0.9	1
Other diseases	38	32.9 ± 0.8	$3,685 \pm 97.4$	8.5 ± 0.46	5.4 ± 0.31	6.9 ± 0.56	6	23.7	3.9	2
Healthy delivered with										
forceps	4	(32.0)	(4,126)	(8.7)	(2.0)	(2.0)	23	-	(3.0)	1

infants of less than normal weight, i.e. the premature infants, suckle less easily the smaller they are. Big infants possess more strength, and therefore they empty the breasts more effectively.

Thus, one must consider these normally active factors when one studies the course of feeding, and when one eventually wants to make comparisons, and draw conclusions, from the results obtained. One of the first tasks will then be to divide the normal material in different ways, thereby trying to isolate the different factors, and establish their respective importance.

As has been shown above, the birth weight of the child is of relatively small importance to the feeding result, as determined by the weight conditions of the infant. This naturally suggests that the infants receive increased amounts of breast milk with increased weight. To investigate this I have made a correlational calculation concerning the total breast milk amount during the 2nd—7th day, and the birth weight of the infants.

The reason for my choosing this period throughout is, that even though the hospitalization period usually lasts ten days, some mothers leave the maternity hospital earlier. This is especially so in the case of mothers with an abundant milk supply, and thus the investigation would yield erroneous results if it comprised a greater number of days. Only 11 mothers and infants in the entire case-material have been sent home before the eighth day. These 11 cases are naturally not included, as the following calculation concerns the amount of breast milk during the 2nd—7th day. The first day has not been included, as only occasional meals were given on this day, the amounts of which were minimal. From the second day onward, the feeding was regular.

The material for these calculations of breast milk amounts, and of the infants' weights at birth, consists entirely of healthy parae, and I have distinguished between primiparae (228), and multiparae (380). The mean weight of the primiparae's babies was 3,426 \pm 27.0 g (see table 3), of the multiparae's 3,636 \pm 24.6 g and the difference thus 210 \pm 36.5 g, demonstrating the greater weights of the infants of the multiparae. The total amount of breast milk during the 2–7 day was a mean of 1,090 \pm 24.1 g for the primiparae, and 1,243 \pm 20.7 g for the multiparae, and the difference 153 \pm 31.7 g.

The correlational coefficient for the breast milk amount and

Total amount of breast milk 2-7 day

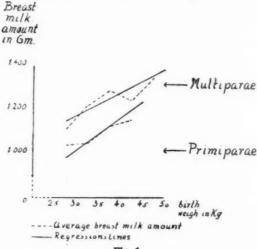


Fig. 1.

the infants' birth weights in primiparae was found to be 0.17 ± 0.06 . Consequently the coefficient is practically equal to 3 times its standard error, and therefore a correlation is highly probable. In the multiparae, the correlational coefficient was 0.13 ± 0.05 and thus more than 2.5 times its standard error. The correlation is probable. Fig. 1 illustrates the regression lines of the changes of the amounts of breast milk (y) with increasing birth weights of the infants (x). For the primiparae the formula $y=0.15 \times +566$ is obtained, and for the multiparae $y=0.11 \times +843$.

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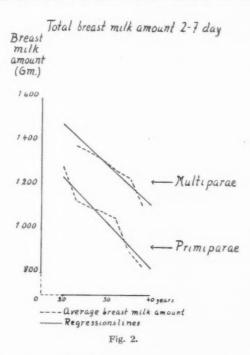
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From this it is evident that the amount of breast milk increases with the birth weight. The stronger infants are able to empty the breasts better. This explains, why the difference in the decrease of weight between big and small infants, and the different times of the weight increase, is relatively inconsiderable.

It is also evident from fig. 1, however, that the regression lines converge with increasing birth weight. The effect of low weight at birth is therefore more noticeable in the primiparae than in the multiparae.



How much then, does the amount of breast milk increase when the infant's weight increases 1 kg? In the primiparae the increase is 150 g pro kg; calculated in percentage at a weight increase of the infant from 3 to 4 kg 14.8 %, and from 4 to 5 kg 12.9 %. In the multiparae the corresponding numbers are 110 g, 9.4 % and 8.6 % respectively.

As has already been mentioned, another systematically active factor concerning breast milk production is probably the age of the mother. A correlational calculation concerning the total amount of breast milk during the 2nd—7th day, and the age of the mother, rendered the correlational coefficient — 0.27 \pm 0.06 for the primiparae, and — 0.22 \pm 0.05 for the multiparae. The correlations are thus negative, and proved. The formulae for the regression of the breast milk (y) with changing age (x), is y = -20.9 x +

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1,659 for the primiparae, and $y=-18.5\ x+1,852$ for the multiparae. In fig. 2 the regression lines and the mean values are represented.

In the primiparae an age difference of 10 years corresponds to an alteration in the amount of breast milk of 209 g. The 20 year old should have a calculated mean amount of 1,241 g, the 30 year old 1,032, and the 40 year old 823 g, the reduction from 20—30 years of age being 16.8 %, and from 30—40 years 20.3 %. In the multiparae the 10-year difference is 185 g, the 20 year old having a mean of 1,482 g of breast milk, the 30 year old 1,297 g, and the 40 year old 1,112 g. The diminuition from 20—30 years of age is 12.5 %, and from 30—40 years 14.3 %. Thus it can be seen that the age is of much greater importance to the primiparae than to the multiparae. Relatively seen, the unfavourable influence for the primiparae also becomes more and more accentuated with increasing age (the reduction of the amount of breast milk is 4.3 % greater than for the multiparae at a change of age from 20—30 years, and 6 % greater at a change from 30—40 years of age).

Thus the capacity of the mammary glands to develop their secreting function is diminished with increasing age. One is perhaps tempted to assume that a certain degree of disuse atrophy is the cause of this condition. A slower action of the secreting properties of the cells is, however, probably of essential importance. This is supported by the fact that the equalizing of the breast milk amount in primi- and multiparae is already established during the neonatal period (see below).

What then is the importance of the mother being primi- or multipara. From table 3 it is evident that the infants of the primiparae lose a mean of 8.4 ± 0.17 %. of their birth weight, and those of the multiparae 7.9 ± 0.12 %. The difference is 0.5 ± 0.20 %, and it is statistically probable. The difference is further proved by the fact that the infants of the primiparae have received additional breast milk in greater amounts than those of the multiparae (11.7 and 6.8% respectively). Further it will be noticed, that the primiparae are 5.6 years younger than the multiparae, which still further proves the difference. The day of minimum weight, however, is the same, (5.2 days).

Thus the infants of the primiparae are apparently worse off than those of the multiparae. This is also evident from the amounts of breast milk, as has been mentioned above. The total amount in the primiparae reached a mean of 1,090 \pm 24.1, and that of the multiparae 1,243 \pm 20.7, the difference being 153 \pm 31.7 g, and thus statistically significant. Thus the primiparae of this casematerial have had 12.3 % less breast milk than the multiparae.

These figures, however, do not exactly correspond to the difference of breast milk amount in primi- and multiparae, because the infants birth weight, and the mothers age, are factors of considerable importance, as has been shown above. In the data used the primiparae were an average of 5.6 years younger than the multiparae, and their infants an average of 210 g lighter.

In addition must be considered the fact that the change of the infants birth weight and the mothers age have a stronger influence on the breast milk secretion in the primiparous. It must therefore be inferred, that the difference in the amount of breast milk in primiparae and multiparae is a factor that is to a certain extent variable.

To give an approximate opinion of how great the difference is, an average case can be chosen, e.g. in both cases a 30 year old mother, and an infant with a birth weight of 3,500 g. With a basis of the average values of the amounts of breast milk, that I have obtained under the circumstances given in this case-material, one can calculate that the primiparae should have a breast milk amount 74 2.7

of
$$1.090 + \frac{74}{1000} \times 150 - \frac{2.7}{10} \times 209 = 1,045$$
 g, and the multiparae $1.243 - \frac{136}{1000} \times 110 + \frac{2.9}{10} \times 185 = 1,282$ g. The primi-

parae has 237 g less, corresponding to 18.5 %. That means that a multipara has about the same amount of breast milk as a primipara who is 10 years younger.

It is also of interest to see, how the breast milk secretion in primi- and multiparae varies day by day during the neonatal period. This is presented in table 4 and figure 3. The breast milk amount of the primiparous is less than that of the multiparous throughout. The differences are statistically established from the 2nd—5th

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Table 4.

Healthy

Breast milk amount in Gm. for each day.

Day	Primiparae	Multiparae	Difference	Percentage less breast milk in primiparae
2	19±1.4	27±1.4	8±2.0	40
3	78 ± 3.6	106 ± 3.4	28 ± 5.0	26
4	172±5.3	213 ± 4.7	41 ± 7.1	19
5	244 ± 5.8	274 ± 4.6	30 ± 7.4	11
6	294 ± 6.0	312 ± 4.7	16 ± 7.6	5
7	313 ± 6.2	332 ± 5.0	19 ± 8.0	6
8	328 ± 6.4	347±5.0	19 ± 8.1	5

day, but not thereafter, and they diminish rapidly from about 40 %—5 %. Thus it seems that the difference present between the primi- and the multiparous, is mostly that the secretion commences more slowly in the latter. As has been shown before, age is of greater importance to the primiparae than to the multiparae. The cause of this is probably that age still further hinders the secretion of the mammary glands. It is not within the scope of this investigation to answer the question whether there is a difference in this respect also later on during nursing, but it nevertheless suggests that the difference is not so great later on. Here one must also observe the factor which reduces the real difference between the primi- and multiparae of these data, and that is the age (the former 5.6 years younger).

It is, of course, interesting to see how imperfect health or illness in the mothers affects feeding results. In this respect I have divided the material into 5 groups (see table 3).

- 1. Mothers with anemia (Hb. according to Sahli < 70 %).
- 2. Mothers with albuminuria (including all cases where albuminuria has been encountered at and after parturition).
- 3. Mothers with resorption fever (only cases with 38° C or more during 3 days).
- 4. Mothers showing other illnessess (acute infections of the upper respiratory passages, trombosis, lymphangitis mammae etc.).

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Breast milk amount per day

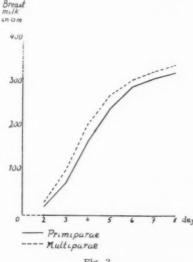


Fig. 3.

5. Mothers delivered with forceps. Ill mothers are excluded. This group comprises mothers who were delivered with forceps because of retarded delivery (primary weakness of labour). One can assume here that the general condition of the mother became worse, and also that the infants could be affected by the lengthy delivery terminated with the aid of forceps.

If one regards the feeding results within these different groups in relation to the infants birth weights (table 3), nothing can be deduced with certainty. There are no positive differences shown relating to greatest loss of weight or loss of weight on the 8th day and no certain differences as to the day of least weight, even if the percentage weight losses are somewhat greater in the infants of the sick mothers than in those of the healthy ones. The loss of weight in the infants of mothers with resorption fever and of infants delivered with forceps (9-9.3 %) is especially noticeable. One must, however, also consider here the additional food which

Table 5.

Differences
between milk amounts in healthy and sick motherson 2nd—7th day.

	Anaemia	Albuminu- ria	Resorption- fever	Other diseases	Healthy mothers delivered with force
Primiparae Quantity %	-82±45.6 -7.5	-82±64.2 -7.5	$-222\pm60.8 \\ -20.4$	-154±56.8 -14.1	-217±87 19.9
Mulliparae Quantity	+40±39.6 +3.2	-82±62.4 -6.6	-84±133.2 -6.8	-138 ± 75.9 -11.1	(—344) (—27.7)

lessens the dissimilarities. Thus, the infants of sick mothers have received a greater amount of additional food.

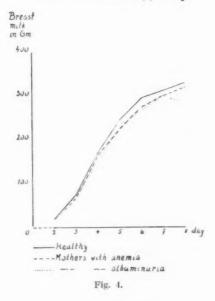
Now if one wants to apply the second rule for the judgment of feeding results, i.e. the amount of breast milk, one must first, of course, divide the case-material into primi- and multiparae. But this is not enough, as the other two factors, the infant's birth weight and the mother's age, also must be considered in a comparison between the group of healthy mothers and the different groups of sick mothers. These two factors are of great importance, as has been shown. In table 3 the mothers' ages and the infants' birth weights are represented as mean values.

The amount of breast milk is estimated from the total amount during the 2-7 day (table 5), and is also shown by a graph (fig. 4-7).

If we first analyse the conditions in anaemia, we find from table 5, that the primiparae with anaemia had $82\pm45.6~\mathrm{g}$ less than the healthy ones, whereas the multiparae with anaemia had $40\pm39.6~\mathrm{g}$ more than the healthy ones. None of these differences is statistically certain. There is no noteworthy difference between the anaemic and healthy groups relating to the mother's age or the infant's birth weight.

In the cases of albuminuria we find that the primiparae as well as the multiparae had somewhat smaller quantities (82 \pm 64.2 and 82 \pm 62.4 g respectively) but no statistical difference can be

Primiparae breast milk amount per day



Multiparae

breast milk amount per day

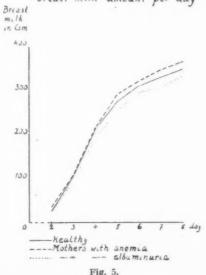


Fig. 5.

Primiparae

breast milk amount per day

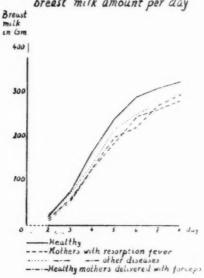


Fig. 6.

Multiparae

breast milk amount per day

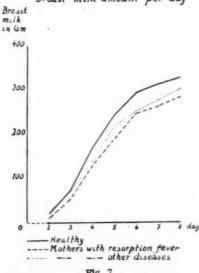


Fig. 7.

proved. Here too, the mother's age and the infant's birth weight are of no account.

Mothers with resorption fever, the group being limited as here (only cases with 38°C or more during 3 days), show a more advanced condition of disease. In the cases of primiparous mothers, which are rather numerous (44), we also find a definite difference in the amount of breast milk (222 \pm 60.8 g). The average age of the mothers, however, in the resorption fever group is 1.3 years higher and consequently the breast milk amount should already be smaller, 1.3

on account of this according to the calculations above $rac{1.3}{10} imes 209 =$

27.2 g. Even if the difference be diminished by this sum, it is still ascertainable. To this can be added that in this group the infants' birth weights are greater than those of infants of healthy mothers, which should increase the amount of breast milk. Primiparae with resorption fever consequently have less milk.

As to the multiparae the case-material is small. The difference in the amount of breast milk amount in mothers with resorption fever and healthy mothers is insignificant.

The group comprising other illnessess is of course a heterogeneous one. The primiparae among these, however, show a smaller breast milk amount (154 \pm 56.8 g), and the difference is practically statistically established. This stands even if the mother's age and the infant's birth weight are taken into consideration, as the effects of these factors practically counterbalance one another (decrease 27.2 g increase 24.8 g).

Multiparae with other illnesses also show a smaller breast milk amount than the healthy ones (138 \pm 75.9). The difference is, however, not even probable in a statistical sense.

Finally we have healthy mothers delivered with forceps. Sixteen primiparae comprise this group. They had 217 ± 87.1 g that is to say 19.9 % less breast milk than those who were not delivered with forceps. The difference is probable, but if corrected with consideration of the mother's age it will be diminished by $\frac{4.4}{10} \times 209$ g = 91.9 g and is then no longer probable. A larger case-material would most probably yield another result.

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On the other hand, if all mothers delivered with forceps (38) are taken as one unit, the difference will be 276 ± 54.3 g and this remains valid also after correction on account of age.

Healthy multiparae delivered with forceps numbered only 4. These too had a considerably smaller amount of breast milk $th_{\rm tot}$ those delivered in a normal way.

In figures 4 to 7 we find the daily breast milk amounts registered, and if we compare the curves of different groups of illnessess with the one for healthy mothers, a notable tendency presents itself. We find that the curves follow each other almost persistently, implying that the difference which exists is levelled more and more as the days pass. The difference in breast milk amount, taken in percentage, decreases. The state of illness has a delaying influence on the commencement of the secretion of breast milk.

In summing up, two essential results of the investigation of the effects of illnesses on nursing are apparent.

Firstly a relatively severe state of illness is required if it is to influence the secretional properties of the mammary glands. Anemia and albuminuria are thus, in the widest sense of the word, of practically no importance. Only such conditions as for example resorption fever (relatively pronounced cases with 38°C or more during 3 days) lower the breast milk amount, as well as other illnessess (infective diseases, local affections of the mammary glands etc.) of more or less the same degree of malignity.

The other interesting fact is that the influence of illness is so much more perceptible in the breast milk secretion of primiparae. The analysis above of the results in the different groups of diseases has shown this and one glance at table 5 is enough to see that such is the case. The decrease in percentage of the breast milk amount is consistently greater in primiparae.

The special position of the primiparae is once again accentuated. Even normally they have a considerably smaller breast milk amount (in this material estimated to 18.5 % during the 2—7 day in mothers of 30 years of age, the infant's birth weight being 3,500 g). In proportion to the infants birth weight we find smaller quantities than in the multiparae, as the infant's birth weight

is lowered. Besides the age of the mother has a much more unfavourable influence in primiparae than in multiparae. Finally diseases are of greater importance in primiparae.

The explanation of this we find in the fact the mammary glands are undeveloped in the primiparae. The secretory function of the epithelial cells is to be taken into use for the first time. The cells have to undergo a certain differentiation which takes more time in primiparae than in multiparae where it is more easily accomplished. Factors which have a negative effect on this process, such as the lesser weight of the infant, greater age and different conditions of illness in the mother, have an effect which is more pronounced in primiparae. All this goes to show why the difficulties are great at the commencement of nursing in the case of primiparae, being not only due to the fact that they are primiparae but also to the fact that the unfavourable factors which influence nursing always have a greater effect on primiparae than on multiparae.

The only factor among those which are of importance in connection with nursing which we can influence, is the mother's age. If a woman gives birth to her first child at a comparatively early age, then this factor is of so great importance to the secretion of breast milk, that the influence of other unfavourable factors, such as the low weight of the infant or possible diseases of the mother, are of less importance. Multiparae have, owing to the fact that they are such, a much better start and unfavourable factors, such as age and disease, are of less importance.

This investigation elucidates a general biological factor of great importance. A pregnancy at a relatively early age is, as experience shows, favourable from an obstetric point of view. The same thing applies, as has been shown here, to the functioning of the mammary glands. From a general physiological point of view an early pregnancy is therefore desirable. Taking a wide view, therefore, society should support early marriages and the generation of children at a comparatively early age.

Finally I wish to illustrate the result of the feeding, at the removal from the maternity hospital, with a table (table 6). It may seem apparent from the figures given above that a large number of infants received an additional quantity of milk at the maternity

Table 6.

The result of the feeding at the removal from the maternity hospital.

Num- ber	Breast		Breast for fants + milk from mother or milk ce	breast other breast	Te pedi hosp	atr.	infant cow's	Breast fed infants + cow's milk mixt.		Artificially fed infant		
	Num- ber	%	Num- ber	%	Num- ber	%	Num- ber	%	Num- ber	0		
1,091	1,011	92.6	20	1.9	14	1.3	45	4.1	1	0.		

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hospital, but this is not the case. Some infants needed an additional quantity only during the first days, others, on the other hand, have been given it even on the last day but then the feeding has proceeded so well that further additional quantities have not been needed. It also happens, however, that additional quantities have had to be prescribed for infants which have not received them during their stay at the maternity hospital.

The data given in the table are based upon the situation at the time when the infants were discharged from the hospital. When doing this I have registered the feeding of each infant in the ledger for maternity hospitals prescribed by the Board of Health. The registration has been made simply by putting Roman figures in the margin: I. breast fed infants; II. a) breast fed infants given an supplementary quantity of breast milk from another mother or from the breastmilk centre, b) breast fed infants sent to pediatrical hospitals for *drawing up* of the breast, c) breast fed infants given a supplementary quantity cow's milk mixture; III. infants not fed by the mother; a) breast milk + cow's milk mixture, b) infants fed artificially.

The sum total of children in this table does not tally with the number of infants which are comprised in the investigation, as all infants with a birth weight exceding 2,500 are included, that is infants of multiparae and infants with diseases. Among the infants discharged 92.6 % have been entirely breastfed, 1.9% have been given the mother's milk + breast milk of other origin, altogether, therefore, 94.5 % have been given nothing but breast-

milk. 1.3 % of the children have been sent to pediatrical hospitals for adrawing ups of the breast and 4.1 % have been prescribed mixed feeding. Only 1 infant has been fed entirely artificially on account of open tuberculosis in the mother and the fact that efforts to acquire breast-milk from other sources were vain. I think that the result can be said to be satisfactory.

It appears to me to be of importance that a registration such as this one, of the feeding of the infant, be made at our maternity hospitals. In that way one would be able to form an idea of how the infants are taken care of at these institutions. It should also be obligatory to enter a short summary of the feeding results in the annals. In such a way one would also obtain an official acknowledgement of the fact that it is not only the mothers but also the infants that require careful medical attendance at our maternity hospitals.

Summary.

1. The case-material comprises 1,074 infants, with a birth weight of more than 2,500 g. 43.9 % of the mothers were primiparae, and 56.1 % were multiparae.

2. With the feeding method used, the infants lost a mean of 8 % of their birth weights. A slight tendency towards increased weight loss, and a later occurrance of the minimum weight has been

established in the heavy weight classes.

3. A probable correlation both for primi- and multiparae could be established between the infants' birth weights and the total breast milk amount during the 2—7 day. The decrease of the breast milk amount parallel to the infant's decrease of birth weight was greater in the case of the primiparae than the multiparae.

4. Certain negative correlation was established between the age of the mother and the breast milk amount during the 2—7 day. In the primiparae an age difference of 10 years corresponded to an alteration of the breast milk amount of about 17—20 %, in the multiparae 12—15 %. The tendency towards a less amount of breast milk in increasing age was greater in the primiparae than in the multiparae.

5. The infants of the healthy primiparae lost $0.5\pm0.20~\%$ more of their birth weight than those of the multiparae, even though the primiparae were an average of 5.6 years younger, and though their infants had received additional food to a greater extent. The primiparae in this case-material had a 12.3 % less amount of breast milk than the multiparae. However, if this is transferred on a similar basis, this difference becomes much greater, e.g. in the case of 30 year old mothers and infants with a birth weight of 3,500 g the difference is 18.5 %.

as

6. Deficient health and illness of the mothers only has an influence on the secretion of the mammary glands when the illness is of a relatively serious nature. Anaemia and albuminuria in the broad sense of the word were practically speaking only of very slight influence. Relatively serious resorption fever and other diseases of comparable seriousness, however, diminished the breast milk amount. The mothers, on whom forceps delivery had been performed also had less breast milk, but the difference, in this case-material could not be proved. The influence of disease was throughout greater in the case of the primiparous than the multiparous women.

7. Conditions applying to the primiparae are particularly noticeable throughout. They have already normally a considerably smaller amount of breast milk, and all the factors that influence the latter negatively, such as low birth weight of the infants, advanced age of the mother, and diseases of the mother have a considerably greater influence in the case of the primiparae.

8. The difference in the amount of breast milk between the primi- and the multiparae is equalized relatively rapidly, so that the differences are small already one week after the delivery. This is the case no matter whether the mother is healthy or ill. The particular conditions of the primiparae must be caused by a slower development of the secretional properties of the mammary glands, a process that is also influenced in a higher degree by unfavourable factors than the corresponding one of the multiparae. This is probably related to the fact that the first differentiation of the cells to their milk producing function is more comprehensive than the later ones.

9. Our only possible way of improving feeding results during the neonatal period, is to work for pregnancy at a relatively early age. The birth of the first child while the mother is young is favourable from the biological viewpoint.

10. The feeding result at the release from the maternity hospitals showed that 92.6% of the infants could be sent home as purely

breastfed children.

11. Registration of the feeding of infants ought to be introduced into our maternity hospitals, and a short summary of the feeding results into the annual reports.

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Infant Mortality in Sweden and in Gothenburg during recent times.

By

Y. ÅKERRÉN.

Table I gives the figures for infant mortality in Sweden from and including the 5-year period 1906/1910 up to and including the 4-year period 1941/44 (the figures for 1945 are not yet available). The rate at which the mortality has fallen during this period is shown in table 2, where the height of the pillars indicates the difference in infant mortality between the adjacent 5-year periods.

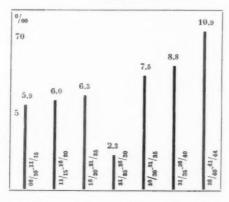
It is of especial interest to note that infant mortality greatly decreased, and at an accelerated rate, after 1930. The favourable development after 1935, and above all after 1940, will probably be very largely connected with the extension and intensification of preventive child welfare, from which an overwhelming majority of infants have benefited during recent years. To a certain extent

Table 1.

Infant mortality in Sweden from and including 1906/10 up to and including 1941/44.

														8.0								
Period																						0/00
1906/10																۰						78.1
11/15								0				0					0		0	0	0	72.2
16/20																				0		66.2
21/25																						59.9
26/30																						57.6
31/35		0	0	0	9	0	۰		0		0		0		0		0					50.1
36/40			×													ě		*				41.9
41/44	0																a					31.0

Table 2.



Difference in infantile mortality in Sweden between the consecutive 5-year periods. The last pillar indicates the difference between the 4-year period 1941/44 and the 5-year period 1936/40.

also the increasing facilities for the care of sick children has played a part. Finally, it is of interest to note that infant mortality continued to fall greatly, in spite of the considerable increase in the birth-rate recorded from and including 1941.

Table III. shows the infant mortality figures for Gothenburg during the years 1936/45. The 5-year period 1941/45 has a lower mortality figure than the period 1936/40. If the figures for the individual years from and including 1943 are considered, it is found that no further tendency towards a reduction of infant mortality can be traced. The figures have become stabilized on a level which is somewhat higher than that for the especially favourable years 1941 and 1942. From the point of view of vital statistics, the number of children born in one year in Gothenburg constitutes such a small group that no great weight should be attached to slight differences in the mortality as between the different years. They may very well be due to chance circumstances. Nevertheless, I considered it to be of interest to try to analyse more closely the infant mortality during the last 10 years. The results are shown

Table III.
Infant mortality in Göteborg 1936/45.

Year	Number of live births	Number of deaths	Infant mortality per 1,000				
1936	3351	116	34.6				
37	3658	109	29.8				
38	4041	138	34.2	30.8			
39	4288	130	30.3				
40	4302	111	25.8				
41	4200	103	24.5				
42	4947	106	21.4				
43	5651	154	27.3	26.4			
44	6021	171	28.4 28.2				
45	6333	183	28.9				

in table IV. Here the deaths are distributed over early deaths, comprising the deaths up to and including the age of 7 days and other deaths before the age of 1 year. The table shows that no tendency towards an increase in mortality after the new-born period can be proved. The small variations in mortality after the new-born period met with during the years 1941—45 will in all probability be fortuitous, and they are very small. No tendency towards a deterioration can be discovered within this group of infant deaths.

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Conditions appear somewhat different within the category of early deaths. Here, as in table III, it is found that the years 1943/45 show less favourable mortality figures throughout than the immediately preceding years. Thus, the 3-year period 1943/45 exhibits throughout higher figures of early deaths than the whole 5-year period 1936/40. Thus, it can undoubtedly be said that there has been a certain tendency towards an increase in early mortality in Gothenburg during the last 3 years.

It appears from the tables that, of the total infant mortality in Gothenburg during recent years, fully 60 % must be ascribed to early deaths. Infant mortality and its future development will therefore be greatly influenced by the success of the campaing against early mortality.

Table IV.

Year	Number of deaths before 7 days	Early de (before 7 o	days)	Deaths be- tween 8 and 365 days	Mortality 8— 365 days per 1,000		
1936	56	16.7)	60	17.9)		
37	50	13.7		59	16.1		
38	84	20.8	16.9	54	13.4	13.9	
39	75	17.5		55	12.8		
40	67	15.6	J	44	10.2		
41	54	12.9)	49	11.7)		
42	61	12.3	1	45	9.1		
43	93	16.5}	16.0	61	10.8	10.4	
44	104	17.3 17.7		67	11.1		
45	122	19.3		61	9.6		

In Sweden, as in a number of comparable countries, early mortality has recently shown a tendency to increase. After a minimum around the 5-year period 1916/20, it rose slowly but uninterruptedly up to the 5-year period 1936/40, when it culminated in a figure for early mortality of nearly 19 per thousand. The decline in infant mortality met with at the same time thus took place in spite of a rising early mortality.

For the period after 1940, only the figures for the years 1941 and 1942 are available at present. They are extremely low in comparison with those of the preceding years. Thus, the figure for 1941 is 16.5 per thousand, and that for 1942 is 14.5 per thousand. The great reduction in infant mortality in Sweden from and including 1941 is thus partly a result of a declining early mortality. It is probably still too early to express an opinion as to whether the decline in early mortality which was recorded for the years 1941 and 1942 is fortuitous or not. It is of interest that at the same time the figures for stillborn infants exhibited a great tendency to fall — earlier, from and including the 5-year period 1921/25, the latter had shown a rise parallel to the rising early mortality, which culminated during the 5-year period 1936/40. One of the causes of the decrease in early mortality and stillborn infants after 1940 is probably the preventive care of mothers,

⁶ Acta pediatrica. Vol. XXXV.

which began to develop rapidly during this period. The measures for the economic support of the less favourably situated expectant mothers, which were carried into effect during the same period, may also be assumed to have contributed towards the favourable tendency in development.

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In view of the general tendency in development in Sweden, conditions in Gothenburg, with the recent stationary or ever increasing early mortality during recent years, are somewhat remarkable. The medical and social-medical conditions which are of the greatest importance for early mortality will be as follows: 1) the care of expectant mothers during pregnancy, 2) care during confinement, 3) the care of the new-born children. In these respects conditions in Gothenburg appear to be favourable. It may be calculated that at least 85 % of all child-bearing women in Gothenburg have received preventive care which can be considered to satisfy modern claims. About 95 % of all the confinements in the town take place in public nursing establishments under the superintendence of well-qualified, specially trained doctors. From and including the later part of the year 1939, regular pediatric consultative activities have been initiated in the maternity wards. Since the same time all premature children have been nursed in a special ward within the maternity ward. This department is under pediatric superintendence. To the extent that it is necessary, cases of illness in the new-born, other than those connected with the prematurity, can receive care at the children's hospital in Gothenburg. Thus, in spite of the apparently favourable conditions, the tendency in development as regards early mortality during recent years in Gothenburg has not been particularly encouraging. This indicates that the campaign against early mortality is none

As a result of these observations I have planned a detailed continuous investigation into early mortality and stillborn cases in Gothenburg. Our intention is to try to analyse during a sufficiently long period, at least 2—3 years, from the obstetrical, pediatric, pathological-anatomical and social points of view, all the confinements which result in the birth of a stillborn child or a child which dies in the period immediately after birth.

The Care, in Sweden, of Polish Infants born in concentration camps.

By

BERTIL ROOS & BIRGER WAHLSTROM.

At the time of the German collapse in the Spring of the year 1945, Sweden had, as is well known, an opportunity to take care of some of the victims of concentration camps. As the result of Count Bernadotte's action over 20,000 prisoners from concentration camps were transferred to Sweden through the Swedish Red Cross during the months of April and May, the majority in a poor general condition and many of them seriously affected by starvation, disease and other privations. During the last week of June and in the month of July something like a further 10,000 displaced persons were taken care of, half of them being bed-ridden invalids. Of these 30,000 so-called repatriands who, through the agency of the Red Cross or UNRRA, could be offered a refuge in Sweden, something like 1 % were children. Amongst the children who were liberated or released from concentration camps, there were also a number of infants. Since these infant cases are very likely unique from various points of view, we thought it might be of interest to mention them briefly to the Nordic pediatricians gathered here.

Of the authors, one (Roos) had chiefly been in charge of the organisation for taking care of the people, and the other (Wahlström) was responsible for care and nursing of the children during their early stay in Sweden.

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The account concerns 43 Polish infants, born in the concentration camp at Ravensbrück, to the north of Berlin. Approximately at the time of the fall of Berlin they accompanied their mothers by the last Red Cross transport from Ravensbrück to Sweden. The children and the mothers filled two of the expedition's omnibuses. Some Polish women far advanced in pregnancy accompanied them, and one child was born in the course of the journey through Germany in one of the 'buses. In one case a woman who had lost her own child had taken charge of another infan, whose mother had died. After a troublesome and laborious journey through northern Germany, they reached the Danish frontier, and the journey through Denmark was then continued by railway. The children arrived at Malmö in the evening of April 28 by the ferry from Copenhagen. As it was almost, or practically impossible to maintain any contact between the Red Cross transports in Germany and Denmark, we received the first news of there being children amongst the refugees, when the ferry was half-way across, We did not find out that infants, and seriously sick infants, had to be taken care of, until the ferry had arrived.

We realized at once that the children were in need of immediate and qualified care and attention. The children's hospitals in Malmö and Lund were fully occupied, and it was impossible to find any other hospitals on the spur of the moment. The only possibility was to place both mothers and children temporarily in a schoolbuilding, which had been got ready for housing adults. A special and separate part of the school was selected, viz. a largish schoolroom was turned into a nursery, and the mothers had to live in two others. The most immediate necessities for the care of the children were procured. Through local aid organisations, children's cots with bedding, infants clothing etc.; and a suitable staff were recruited. The children could now have a closer examination, and it was found that the majority were in a more or less advanced stage of malnutrition, many of them also suffering from diarrhoea and strongly disseminated skin-diseases. Through the kindness of the head doctors in charge it was made possible during the first few days to remove 11 of the most serious cases to the children's hospitals in Malmö and Lund. Six of these died

within a few days, and the cause of death in these cases was malnutrition together with infections of various kinds.

Proper nursing had also to be organised for the other children. On inspecting the new children's section at Landskrona it was found that it had only recently been completed and was about to be opened. The section was also placed at our disposal by the county authorities' hospital administration. After the equipment had been supplemented in some respects, and a staff provided, the children were moved from the temporary camp to the children's section at Landskrona. This was on May 3rd, 41/2 days after arrival in Sweden. The children's section, which has officially 25 beds, was able to accomodate 36 infants, and to this were later on transferred the survivors of those children who had previously been quartered at the hospitals in Malmö and Lund. The ward was also used for two Polish refugee children born in Sweden and in need of nursing. Later on other sick refugee children were also taken into this section. The last Polish infants were not discharged until the month of December, 1945. The mothers of refugee children were living in temporary premises within the hospital grounds, and this facilitated the nursing of the children.

A mothers' home was established in a villa in the town of Landskrona, and as soon as the condition of the children permitted, mother and child were transferred to the mothers' home. This housed something like 20 mothers and the same number of children. Some were later on transferred to a similar home in the southern part of the county of Småland.

On arrival in Sweden both children and mothers were carefully examined. Inter alia the mothers were X-rayed, but only in one case was a suspicion of tb. harboured, and this seemed remarkable in view of the high frequency of tbc amongst other groups of adults from the concentration camps. After 2 months, renewed X-ray pictures of the mothers were taken for the sake of safety From these the first tb-changes in two of the mothers at the mothers' home were discovered. Fortunately, none of the children in the home had had time to become infected.

Apart from the previously mentioned infants who died of malnutrition, two died of th miliaris, 22 and 90 days respectively

Table I.

Children who were only breast-fed, or chiefly so.

(d=days, w = weeks, mo=months).

		on	en	al den		ight af Swe	ter stay den of	in			
ż	sex	Age on	Sweden	Weight on arrival in Sweden	14 days	1 month	2 months	3 months	Remarks		
1	m.	5	w	3,560		4.200			Healthy but scabies		
2	m.	7	W	3,220	3,420	3,800			0 0 0		
3	m.	3 1/2	mo	4,720		5,400			b b b		
4	m.	3	mo	3,300	3,500			6,500	Mother the, child Calmettevace.		
5	f.	2	w	2,610	2,900	3,400	4,600				
6	m.	2 1/2	w	2,810	3,020	3,600					
7.	f.	5	w	2,460	2,560	3,150	3,900	4,850	Mantoux pos. X-ray pulm: 0		
8	f.	6	w		3,200	3,480	4,000	4,650			
9	f.	6	w	3,300	3,460	3,800	4,400	5,200			
10	m.	5	w	2,500	2,730	3,000	3,250	4,400	Abscesses, pyodermia		
11	f.	5	w	3,200	3,600	4,000	5,300				
12	m.	5 1/2	w	3,300	3,430	3,600	4,600		Enterocolitis		
13	m.	6	w	3,790	4,000	4,700	5,600				
14	f.	6	w	2,700	2,850	3,280	4,000		Congenital stridor. dia thesis exsud.		
15	m.	6	w	3,100	2,850	3,200	4,300		Abscesses		
16	f.	7	w	2,960	3,200	4,100	5,200				
17	f.	7	w	2,680		3,500	4,200	5,300	Mantoux. pos. X-ray pulm: 0		
18	f.	8	W	2,800	3,000	3,400	4,600				
19	f.	8	w	3,310	3,500	3,980	5,200		Mantoux pos. X-ray pulm: 0		
20	m.	2 1/2	mo	4,930	5,000	5,400					

after arrival in Sweden. A synopsis of the 8 cases which terminated in death, is given in Table III.

35 children survived. One mother had died on arrival in Sweden. In addition, as stated, there were 2 Polish children who were born in Sweden; one of them the day after the mother's arrival (this child was premature, with a weight of about 4 pd

Table 11.
Children fed only artificially.

		on I in en	on i in en		eight af Swe	eden	y in				
Z	sex	Age on arrival in Sweden	Weight of arrival in Sweden	14 days	1 month	2 months	3 months	Remarks			
21	f.	10 d	2,420 g.	2,680	2,800	3,500					
22	f.	5 w	2,480	2,700	3,200	4,300					
23	m.	2 w	2,100	2,200	2,400	3,200	4,400	V. O. C. congen			
24	m.	17 d	3,400	3,500	3,600	4,600	4,700	Encephalitis, dyspepsia			
25	m.	4 w	2,770	3,050	3,300	4,000	4,650	Dyspepsia			
26	m.	4 w	2,950	3,200	3,600	4,000		Carriers of diphteria bacill.			
27	m.	5 w	2,200	2,600	2,900	3,800		Otit. supp.+of diphte-			
28	f.	5 W	2,160	2,200	2,160	2,900	4,000	Bronchitis. Meningitis (pneumococci)+periostitis (salmonella).			
29	f.	5 ½ w	2,150	1,980	2,400	3,300	4,280				
30	m.	6 w	2,500	2,700	2,900	3,900	4,800	Bronchit. Abscesses. V. O. C. congen.			
31	f.	7 w	2,500	2,700	3,000	3,800	5,400	Meningitis (pneumo- cocci)			
32	m.	8 w	2,990	3,100	3,500	4,300	5,000	Osteomyelitis of tibia			
33	f.	7 w	2,310	2,550	3,000	4,100		Enterocolitis			
34	m.	2mo 3v	2,640	2,610	3,200			Dyspepsia			
35	f.	3 w	4,080	4,300	4,850			Osteomyelitis of tibia			

at birth) the other was born fully one month later and weighed then about 6 pd.

20 children were brought up exclusively or nearly exclusively, by given breast from their respective mothers. These children are given in Table I. 9 children were given a high percentage of mother's milk together with artificial food. The remaining children received only artificial food. Citric acid milk was used, diluted mixtures to start with, but soon undiluted was given. All the mothers and children were also given AD-Vitamines and C-Vitamines. A synopsis of the children who were given artificial nourishment, wholly or principally, is mentioned in Table II.

Table III.
Children dead after arrival in Sweden.

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Nr	sex	Age on arrival i Sweden		sta	h after ny in reden	Cause of death			
36	m.	6 w.	2,525	1	day	Malnutrition			
						(Inan. extren	n.)+broncho-		
							pneumonia		
37	f.	2 1/2 mo	2,050	2	days				
38	f.	3 w.	1,720	2	days		+bronchitis capillaris		
39	m.	5 w.	2,230	2	days		+ bronchitis		
40	f.	5 w.		8	days				
41	m.	6 w.		18	days				
42	m.	2 mo		22	days	tbe. miliaris			
43	f.	2 mo	2,000	90	days	tbc. miliaris			

All the children except 3 suffered during the first few days from typical hunger-passages, and were more or less under weight (see the tables) and in a high degree of dehydration. All the children were, on arrival, suffering from scabies and disseminated intertriginous changes. It was not until after repeated scabies courses for both children and mothers simultaneously, that the children were free from skin-disease. At the beginning all the children suffered from ordinary rhinopharyngitis.

Amongst the surviving children there occurred also the following more remarkable diseases:

Encephlitis (with increased albumen in liquor and trifling increase of cells): 1 case. Meningitis (pneumococcal type) 2 cases, of which one developed pronounced hydrocephalus. Osteomyelitis: 2 cases (caused by salmonella, paratyphus C, with localisation in the tibia in both cases, which healed gradually without leaving any injury). Vitium organicum cordis congenitum + dystrophia: 2 cases. Bearers of diphtheria bacilli: 2 children together with their mothers; free from bacilli after 2—3 months.

The mothers supplied in the course of conversation, in turn and through an interpreter, information about the social conditions not only prior but also during captivity, and of the conditions in the concentration camp at Ravensbrück, (some had also been to Auswitz). The following information is given from these statement:

9 mothers were of the ages 30—36 years, of these 8 married before their captivity. 7 of these had previously 1—3 children. 1 mother was 18 years old, the remaining ones 20 to 25 years, the majority 20 to 22 years.

With one exception the women may be considered as having conceived at home. All except one had been removed from their homes in the neighbourhood of Warsa at the end of August—the beginning of September, 1944. They had first been put to digging, the erection of airports and ammunition works, etc. and then in the majority of cases 2 to 3 months before parturition they were taken to the collective camp at Ravensbrück. A few had gone there 2—3 weeks before and two of them had obtained work at a factory until their water broke just before parturition.

The average weight of the mothers on arrival in Sweden was 50 kilos. Some few bore marks of illtreatment. By far the greater number were in comparatively good condition, compared with other refugees who arrived simultaneously from concentration camps. But these mothers had been there for a comparatively short time, about 8—9 months.

During their stay at Ravensbrück at 4 or 5 in the morning, a roll-call took place and then both pregnant women and mothers, even those who had just recently given birth to a child, had to stand barefooted on cement floors, dressed only in their underclothing, until 7 a.m., when they were given some soup. As to the food, this seems to have been the same as in other camps, which has often been discussed, so we will not discuss this futher.

On parturition the women were taken to a so-called *revir*-hospital block: there were 24 of these in the camp with accommodation for 30 to 40 persons in each. Both women and men (the latter described as medical men) assisted at parturition. No suturing in the case of perineal defects or sphincter ruptures in the mother, ever took place. Nor was any narcosis given, of course. After 24

hours the new mother had to get up and go and take the child with her to one of the barracks. 300 lived in each barracks, with two mothers and their children in each cubicle. Every night a few children died, usually 10 to 12 each night. 2 kettles of warm water once a week were handed out which were to be used for cleaning and it had to be sufficient for all the mothers. Clothing for the children was obtained during the last few months, when the regulations were not quite so severe, by exchanging the bread (which was distributed once every day) for old clothes from the stores. *One got quite a good deal for one week's bread rations.

As far as is known, these are the only infants that have come from a concentration camp. The mothers relate that at 2-3 months their milk as a rule left them. From the camp kitchen they received so-called »schleim» (sludge) for the children; they never got to know how this was prepared. But all who were fed on it soon suffered from diarrhoea, their bellies swelled, and after a short time they died. The mothers never saw any children over the age of 4 months in the camp (if a child was still alive then, a couple of women informed us, it was killed). 4-5 months after parturition the women were removed, the remaining mothers never discovered where.

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(Following the lecture a film of the children's arrival in Sweden, and some photos showing various periods of the children's stay in Sweden were shown.)

Mental injuries due to hospitalization or custody in children's homes.

By

G. KLACKENBERG.

Published in Sv. Läkartidningen nr 45/1946. The following is merely a short résumé.)

Neurotic symptoms and difficult behaviour sometimes appear in children following their stay in hospital or a children's home and the condition may subsequently be aggravated through an unjudicious attitude on the part of the parents. The author illustrates his thesis with cases exhibiting tics, anxiety states, enuresis and enkopresis, retarded speech, excessive masturbation, aggressiveness, etc. The reason for the disturbance is sought in the fact that the child's dependence on its environment, especially the mother, is founded on emotional rather than intellectual reactions at the age of 1—3 years and that the feeling of forlornness and exposure experienced by the child becomes a dominant factor. Frightening and painful examinations and courses of treatment are of course contributory factors in the causation of anxiety states.

Careful selection of the cases sent to hospital at this age is recommended as a prophylactic measure. Moreover, the reception and treatment at the hospital should be less routine-bound and tinged with more human tenderness, and the parents should be instructed how to treat with understanding and love such disturbances of behaviour and clinging ways as may have developed in the child during its absence from home.

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Child Welfare Work in Denmark.

Lecture introducing the film . The Future of the New Generation .

By

AAGE BOJESEN.

Chief Physician to the Child Welfare Centres of Denmark.

I am grateful to be given the opportunity of showing, at the 8th Nordic pædiatric congress, a film about child welfare work in Denmark; the film was initiated by the group within the Danish Child Welfare Committee which works especially for the kindergartens. By means of this film I hope to show my Nordic colleagues what is being done in Denmark for our children at the centres for the care of infants, in crèches, day homes, kindergartens, places for children's playtime, etc.

The film was entitled "The Future of the New Generation" because we were of opinion that the preventive care of little children is a link in the comprehensive prophylactic work done so that the children may grow up healthy in both body and mind. We try to give the child a fair start by caring for it from its birth at the centres for the care of infants, when they are quite small, in crèches and in day nurseries. When the Children are older, there are the kindergartens, day nurseries and places where they may spend their playtime, so that the child is not left alone, and by visting the day nurseries and clubs may avoid the bad influence of playing in the streets and in the yards between the big houses in town.

Moreover, it is very important that child welfare work should help the housewife by looking after the children while the mother is at work; thus the committee is helping in the maintenance of the home.

In Denmark there are 60 day nurseries for infants with 2027 cots, 327 kindergartens with room for 15977 children and 75 places for children's playtime with room for 4562 children.

There is a great deficiency of preventive institutions, not least in Copenhagen, where it is impossible to receive all the children who apply.

The preventive institutions for the protection of children are nearly all initiated privately, by friendly societies. The earliest institutions for the care of infants were started in 1908 by the Parochial United District Nursing Institutions as a part of the fight against infant mortality; the first creche was started in 1822 in Copenhagen; kindergartens and day nurseries were started in 1850 in accordance with the Fröbel principles on the bringing-up of children, and the first home for children in their playtime hours was started at Odense in 1804.

At the present time both the state, the boroughs and the urban districts have stepped in to help with subsidies, and by the statute of 29th of June 1945 financial assistance was given to the kindergartens and creches, amounting to 30 % of their annual expenditure and in cases where the local authorities give a subsidy of 30 % the state gives a further 10 %.

There are thus now far better conditions for kindergartens and creches than there were previously.

There are those who are of the opinion that by putting the children into preventive institutions the parents' responsibility is lessened. But that is not the case at all. For, besides looking after the children while the mother is at work, an attempt is made to co-operate with the parents by meetings of and for them to start summer colonies for the children, and so on.

Thus it is of the utmost significance that the daily work at the preventive institutions be performed by skilful and fullytrained women, and in the homes and clubs for children in their playtime hours perhaps by men as well.

For this training there are in Denmark 5, trainingschools ε_Γ high-schools, where the pupils are given a 2-year training in order to be a teacher in a kindergarten.

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Unfortunately a quite insufficient number of kindergarten teachers are trained each year, which is one of the reasons why we dare not start as many preventive child welfare institutions as are needed, since it is essential that their assistants as well as the teachers themselves be fully-trained kindergarten teachers, because, among other things, pedagogic training is of decisive inportance for the running of, and work in, any preventive institution.

In this film it is therefore attempted to give an impression of the training of the would-be kindergarten teachers.

The film shows, at the beginning, the work at a centre for the care of babies and in order to give an idea of this prophylactic work I will merely state that the parochial district nursing in Copenhagen have 36 centres for the care of infants with 45 physicians, 22 of whom are trained children's doctors, the rest are assistants with training in pædiatrics.

During the last year 70 % of the Copenhagen children have been to the centres during their first year, and there have been in all 38069 conslutations at the 36 centres.

In the town of Greater Copenhagen there are 44 centres for the care of babies but only a few centres in the remainder of the country.

The centres are in close co-operation with the shealth nursess who work in the homes but who also visit the centres which were originally advisory centres for nursing mothers; now they are also chield welfare centres where the children have 4 examinations during their first year.

Furthermore, the film shows pictures from the old crèche staircase where the children used to sit on the stairs under the eye of the *crèche-mother*. Then it shows pictures from of the work of the late Miss Anna Wolff; who was a pioneer in kindergarten work; teaching in the slums.

Besides the training of would-be kindergarten teachers the film shows a doctor's examination and a dentist's work in a kindergarten.

There are pictures from large, modern institutions with both creches, kindergartens and playtime homes, and there are pictures from small institutions with about 50 children, and from one of the emergency kindergartens instituted during the war as an emegency measure on account of lack of room, and also pictures that show under what unhealthy and bad conditions thousands of children are living in the slums of the city.

Some typical child welfare institutions in the provinces are shown — creches, kindergartens and playtime homes, and you will see what splendid child welfare work is being done in the Danish provincial towns.

The film ends with a small colour film showing Her Royal Highness Crownprincess Ingrid and the two little princesses Margrethe and Benedicte at the Castle of Graasten in Slesvig.

Crown Princess Ingrid feels the most lively interest in the Children's welfare work in Denmark, which the Princess shows in many ways, not least by being protectress of the Children's Welfare Committee, a big institution which works for the initiation and development of preventive institutions, especially in new buildings.

I do hope that the congress members, when they have seen this film, will have received an idea of what is done i Denmark for the children by the children's welfare institutions as part of the work to help the rising generation in Denmark.

Discussion on Paper 6-10:

LEPPO: Preventive care of children in Finland.

Considerable progress in child welfare has been recorded in Finland during the last two decades. Credit is due to the Mannerheim League for Child Welfare, the Chairman of its Executive Committee, Prof. Ylppö, and the societies »Mjölkdroppen» and »Folkhälsan i Svenska Finland» for having, in the main, promoted this development. Already before the socalled swinter campaign» in 1939—40, about 140 child welfare centres had been established, mainly on the initiative of these societies. In 1921 the Mannerheim League founded a Child Welfare Institute, the »Children's Castle» in Helsingfors, which has played an important part in the organization of child welfare work on modern lines in our country.

As a result of the improvement in the standard of nursing and better

hygienic conditions, the infant mortality has decreased by one half in relation to the figure registered at the beginning of the century. This improvement was slower, however, than in the other Scandinavian countries. In 1937 the infant mortality in Finland was 69 per thousand liveborn children and Finland ranked as No. 11 among the 30 states of Europe.

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The war which has now come to an end revealed considerable deficiencies in the care of children, especially in rural districts. Since 1930 a service of travelling Child Welfare centres, working in specially equipped cars, has been in operation. This work was initiated by the Finland Relief Inc. and was later taken over by the Mannerheim League. About 100,000 children have been examined by the medical attendants of this service, who have been able to record a large percentage of anemia and rachelis cases, chiefly due to faulty nursing and ignorance. Improper food due to war-time conditions also accounted for the prevalence of these ailments. Thanks to the consultative work of the Child Welfare centres during he war, the use of cod liver oil and vitamin D has become widely spread and advanced stages of these illnesses are now rarely met with.

The past years of walfare have brought about an acute realization of the necessity of promoting public health and especially child welfare in our country. The State was moved to take an interest in these problems, and on July 1st, 1944, three laws were passed which had an important bearing on the care of children in particular. These were 1) the law enjoining rural and municipal communities to maintain child and maternity welfare centres, 2) the law providing for a service of midwives in every rural or municipal district, and 3) the law ensuring the maintenance of rural and municipal Public Health nurses. The first law stipulated that within five years from its institution, i.e. by 1949, every township, small urban administrative unit and rural district should have established at least one child and maternity welfare centre. The State shoulders the costs of journeys undertaken in the course of duty and the remuneration of medical attendance calculated on the number of consultative office hours and the number of cases attended to, and also provides 3/4 of the foundation funds. The local communities stand for the remainder of the costs. At the end of 1945 there were 367 central consultative stations in our country. permanently established in their own set of rooms, and 473 so-called auxiliary stations working in temporary offices. We have thus at present altogether 840 consultative offices in Finland, employing 330 doctors and about 600 Public Health nurses.

The State Medical Board has prepared health-cards and modelinstructions for use in the Child Welfare centres. The Mannerheim League is now planning the issue, in collaboration with the State Medical Board, of a series of new leaflets containing advice in child-welfare matters, which will be distributed to all stations, together with corresponding instructions.

The infant mortality has diminished somewhat in the last few years in spite of the war. This decrease is no doubt due to the recent intensified work aiming at the establishment of a system of advisory centres. The infant mortality figure for 1945 was 63.

Child welfare work in Finland has made a good start and we can with confidence look forward to favourable results in the future.

Ström: Since 1938, when State-organized child welfare work was initiated in Sweden, the preventive care of mothers and children has progressed rapidly, even during the years of the war. The organization was completed in 1945 throughout the country. In 1944, the last year for which complete statistics are available 55 % of the mothers, 79 % of the infants, 47 % of the 1—2 year old and 11 % of the 2—7 year old were examined. In Stockholm and Hälsingborg the organization has been extended to include all children under school-age. Free travelling for doctors, midwives, nurses, and the members of the public concerned, has lately been introduced and free treatment with preventive medicines was already adopted at an earlier stage.

For a more detailed exposé see »Nordisk Medicin» 1946.

RINVIK: In connection with Dr. Ström's lecture and Dr. Leppo's account of Child Welfare work in Finland during the war, Dr. Rinvik pointed out that due attention should also be paid to the *quality* of the mother's milk. An often recurring warfime experience in Norway was that even full-term infants who were exclusively breast-fed did not thrive and put on weight properly, although the diet of the mothers should have ensured a sufficient milk supply. Signs of rickets were even observed in those cases and, as a result, cod liver oil was given to the infants from the age of four weeks, besides breast-milk.

Factors influencing the risk of complications in scarlet fever.

By

NILS FAXÉN.

In about 17,000 cases (the scarlet fever cases at the hospital for contagious diseases in Gothenburg 1918—1943) the riskfigures for the common complications have been computed during the first five weeks of the disease. The risk of developing otitis is at its height in the first week; lymphadenitis and nephritis, however, in the third week. The risk of developing a new exanthema does not decrease during the first five weeks.

To this material the cases during the years 1944 and 1945 have been added (total number about 19,000 cases) and the influence of season, various epidemics and the number of patients in the wards (the number of patients in proportion to the number of beds reserved for scarlet fever) has been studied. The seasonal variations were very small and no statistically significant differences could be found. The epidemics in 1927—1945 showed far greater risk-figures for nearly all complications than the other epidemics and the periods without epidemics. A large number of patients in the vards seems to increase the risks of the development of lymphadenitis and nephritis.

The results of the investigation will be published fully later in Acta Paediatrica.

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On the Prognosis of reumatic fever.

By

ERIK G. JACOBSSON.

The author has made a follow-up examination of 689 cases, who previously had been treated for rheumatic fever in the Childrens' Hospital of Gothenburg in the years 1922-1940. It was noted that the number of chorea minor cases (as a primary manifestation of the rheumatic fever) show a decrease towards the end of this period. The number of more severe cases of rheumatic fever also seems to decrease to a certain extent during these years though this could not be proved to be statistically significant. An analysis of the primary mortality and the total mortality up to the year 1945 shows a clear and obvious decrease of the total number of lethal cases as well as those taken in the percentage of all rheumatic fever cases. The probable cause of this improvment of prognosis is considered to be, except for a possible change of genius epidemicus, a very distinct and statistically almost significant tendency in recent years to hospitalize children in an earlier stage of the disease than was done in previous times.

This investigations will be published more fully in Acta Paediatrica, Vol. XXXIII. Suppl. VII

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Antistreptolysin titer and Sedimentation rate in Polyarthritis and Endocarditis in Childhood.

By

RURIK THELIN.

Haemolythic streptococci form, as is well-known, toxins, one of which is streptolysin. This is an antigen producing an antibody, antistreptolysin, which was first shown by the Englishman Todd in 1932, who has also worked out a method of measuring antistreptolysinititer (Asl) in serum. Also, Todds standard serum is used all over the world. The quantity of antistreptolysin in serum is expressed in antistreptolysin units and such a unit is equal to 1/20000 of Todds standard serum. The number of antistreptolysin units is called antistreptolysin titer (Asl).

Many bacteriologists have since then examined Asl in different diseases, among others Coburn in America, and here in Scandinavia the Dane Kalbak and the Swede Winblad. The latter two have inter alia made investigations relating to acute polyarthritis in adults and they have also fixed the normal value at 200 units.

As haemolythic streptococci probably belong to the most videly spread human bacteria, one vould expect to find an increased Asl in a large number of patients of any average case-material. Kalbak found, however in patients of all kinds aged 11—80 years an Asl increase of 6 % only whereas in an age-group of 0—20 years Asl was increased in 16 % of the cases. Kalbak points out that this confirms the clinical experience that streptococc diseases

are most common among children and young people. Kalbak and Winblad are of the opinion that an increased titer shows that an infection of haemolythic streptococci is in progress or has existed a short time previously. Repeated increased values indicate that the infection is still in progress, which is possible without any clinical symptoms being visible. Declining values indicate that the infection is decreasing or has disappeared.

In this way it is possible to get a certain idea of the activity of the infection. In acute rheumatic polyartritis Winblad found increased Asl in about 85 % of the cases. Sometimes there was a high titer even at the beginning of the rheumatic attack, which is supposed to be due to the fact that in most cases the patient has had an angina or other infection 2—3 weeks before. In some cases the titer was instead quite normal or moderately increased for 1—3 weeks. In the relation between Asl and sedimentation a certain parallelism was found. Nevertheless the sedimentation was nearly always at its highest even in the first days, whereas the antistreptolysine could at the same time as mentioned, be low. On the other hand the sedimentation sank in a shorter time and the antistreptolysine could be high for several months. It is generally held that the risk for a recurrence is not over until the titer tends towards normal values.

During the last year we have, in the Pediatric Clinic of Lund, examined a number of cases of acute polyarthritis and endocarditis showing Asl as well as sedimentation, and the results obtained are the same as in the adult case-material mentioned above.

The patients, aged 4—13 years, show all, with only one exeption, typical symptoms of polyarthritis and all show signs of endocarditis. Most of them have had some infection, 1—3 weeks before falling ill, some of them recurrent anginas.

In most cases the titer is moderately increased with values up to 300—500 during the first week after the onset of the illness, whereafter it increases strongly for 1—3 weeks, in one case up to 3000. For another 2—4 weeks it then declines to about 400, remaining constant for some weeks or months, before sinking to a normal level. The sedimentation, which is a microsedimentation according

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to Landau, decreases rather rapidly after the beginning of the disease and is already normal after 3-5 weeks.

In some cases the Asl is high, even at the beginning of the polyarthritis, (700—1000 units) and can then rise further, before it goes down to about 400. In these cases the sedimentation also went down in a few weeks. In other cases the titer was the whole time about 500, before finally dropping to normal. In all cases increased Asl was found for several weeks after the sedimentation had become normal. As yet the examinations extend over too short a period to allow definite conclusions to be drawn from them.

However, Asl seems to be a valuable adjunct to other examinations of acute polyarthritis and endocarditis even in children. Increased values indicate that a streptococcus infection is going on or has recently been in progress, and one gets a certain idea of the virulence of the infection as well as of the natural immunity of the body. Also for the diagnosis Asl seems to be valuable. Thus, if only insignificant symptoms of endocarditis are visible and no joint lesions, then high values of titer, especially repeated ones, indicate a rheumatic genesis. Low values, however, do not exclude such a genesis.

Even if sedimentation, temperature, electrocardiogram and physiological tindings seem to indicate that polyarthritis and endocarditis are healing or already healed, it is probably advisable to be very careful during the convalescence, if the Asl remains high. One of our cases had 4 low sedimentations and a normal electrocardiogram and temperature and would have been allowed to be up if Asl had not been so high as 1100. After a month the patient got a recurrence of his polyarthritis. This may possible indicate that Asl is not without importance as a prognostic aid in forming a right opinion of rheumatic polyarthritis and endocarditis in childhood.

Discussion on Paper No. 11-13.

BOJLEN: I wish to thank Dr. FAXEN for his paper. In this connection I should like to draw attention to Dr. Jersild's account of results obtained with penicillin, which is even now being laid before the Congress in Gothenburg.

Dr. Jersied has treated 60 scarlatina patients subcutaneously at the Blegdam Hospital in Copenhagen with 60—100,000 units of penicillin, administered three times in 24 hours for a period of 6 days (0.3 cm³ 1°/00 adrenalin 5 cm³ physiological salt water + Penicillin). After this period the patients were removed to a scleans ward.

Of the 60 patients thus treated 59 were free from streptococci when discharged (4 weeks later). One had hemolytic streptococci of type C.

Three days after the beginning of treatment 54 of the patients were already streptococcus-negative. After 6 days 58 were streptococcus-negative and 2 were positive. None of the patients thus treated developed any complications.

For the sake of comparison Dr. Jersied also treated 60 scarlatina patients with sulphanilamid; when discharged at the end of four weeks, 34 of these were streptococcus-positive and 9 were negative (7 were not examined). 26 of these cases were of a complicated nature, 34 escaped

complications.

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Moreover, Dr. Jersied treated a group of 18 scarlatina patients with the above described Penicillin doses for three days. After 3—4 days all the patients were streptococcus-negative, but on the 5th day four were again positive, after two weeks 11 and after three weeks 13. When discharged after four weeks half of the patients were positive. 7 of the 18 patients suffered from complications.

The above seems to indicate that the hospital stay could be reduced to 8—10 days by means of a six-day treatment with the dose tested by Dr Jersild.

FAREN: At the Hospital for Infectious Diseases in Gothenburg an investigation into the use of penicillin treatment for scarlatina is being carried out under the supervision of Thulin (Lund). Streptococcus-free patients undergoing after-treatment have been removed to a *clean* ward. Very few complications seem to set in in this ward.

FAXEN: It might be contended that risk-figures should have been used in the computations instead of percentage mortality figures.

Jacobsson: I merely wish to point out that the follow-up examinations were performed four years after the primary onset of the illness. At that time most of the deaths had occurred, as shown by the blockdiagram, and the comparison of the curve for the primary nortality with that for the total mortality thus ought to be fairly adequate.

PLUM: Referred to KALBAK's accounts of the Streptococcusagglutinin reaction observed in investigations carried out by him. The reaction proved to be positive in cases of Chr. Polyarthritis and negative in Febris rheumatica, whereas the position was reversed as regards the Antistreptolysin reactions.

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A summary of 100 treated cases of tuberculous coxitis.

By

WALTER RISINGER.

100 cases of tuberculous coxitis have been considered in relation to statistics. Tuberculosis of the hip-joint appears to be nearly as frequent as spondylitis and represents half the affections of the hip-joint. The diagrams showing the commencement of illness and the admission to hospital show a considerable difference because of difficulties in diagnosis, and a long period of waiting before admission. The maximum age for the commencement of the illness appears to be 7 years, the same result as SORREL obtained in his statistics of 1000 cases. The source of infection has been discovered in 41 cases; in 38 cases it was found to be inside the family, and in 3 outside.

8 cases have been followed up from erythema nodosum to the first local symptoms and gave an average incubation period of 1½ years. 29 cases have no pulmonary processes, 53 have tuberculosis of the hilus, 3 pleurisy and 3 pulmonary tuberculosis.

Traumatic genesis is proved in 17 cases.

Isolated tuberculosis of the capsule and the synovial membrane is uncommon.

The process usually develops foci in caput, the neck and acetabulum until acetabular protrusion.

The average time at hospital is 2 years, but may be 6-10 years.

The patient must be symptom-free 5 years to be declared sound and still that long period does not give a guarantee against recurring abscesses.

General light and open-air treatment are important and so are school attendance and diverting work.

Local treatment in plaster in a good position is necessary as a rule. The joint becomes anchylotic after 1—2 years and then the patient is given a bandage of plaster and later on of leather for walking.

Anchylosis can be obtained surgically by extra-articular or intra-articular arthrodesis. The latter means joint resection. By the extra-articular arthrodesis trochanter is connected with the epiacetabular part of os ilium with a bone-graft from tibia, femur or os ilium or an artificial os purum graft with surrounding os novum.

A bad position often makes osteotomy necessary and the subtrochanteric method has been preferred.

60 cases have been subjected to surgical treatment: 14 extraarticular and 2 intra-articular operations, 20 extirpations of fistulae and abscesses and 23 osteotomies.

Die Tuberkulosefrekvenz nach exsudatioen Pleuritis bei Kindern.

Von

H. H. NATHORST.

Es wurden 595 Kinder im Alter von 1—6 Jahren, die wegen Pleuritis exsudativa während den Jahren 1922—1938 hospitalisiert waren, nachuntersucht. Die Beobachtungszeit lag zwischen 5—22 Jahren.

1. Das Risiko an Pleuritis exsudativa zu erkranken ist grösser für Knaben als für Mädchen. Die Wahrscheinlichkeit für Mädchen in Göteborg an Pleuritis exsudativa zu erkranken ist $6\,^0/_{00}$, während sie für Knaben $9.3\,^0/_{00}$ beträgt, wobei dieser Unterschied statistisch sichergestellt werden konnte.

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2. Von 460 an Pleuritis exsudativa erkrankten Kindern wurden die Röntgenfilme durch einen Röntgenologen und den Verfasser durchgesehen. Dabei zeigten 78 % pathologische Veränderungen im Hilus oder Lungenparenchymveränderungen oder beides zusammen. In 92 % fanden sich die Veränderungen auf der gleichen Seite wie die Pleuritis.

3. Von den 595 Kindern erkrankten später 122 an einer Tuberkulose. Dabei beträgt die Wahrscheinlichkeit an Tuberkulose zu sterben nach 5 Jahren 4.7 %, nach 10 Jahren 6.5 % und nach 20 Jahren 11 %. Die Wahrscheinlichkeit an Lungentuberkulose im gleichen Zeitabstand zu erkranken beträgt 6 %, 10 % und 16 % und an einer extrapulmonalen Tuberkulose zu erkranken 5.7 %, 7.8 % und 9 %. Die Wahrscheinlichkeit später eine Tuberkulose zu bekommen ist kleiner für Kinder, die vor dem 10. Altersjahr ihre Pleuritis exsudativa bekommen haben, als wenn sie später erkranken.

Eine ausführliche Publikation in den Acta Paediatrica wird folgen.

Studien über kongenitale Lues in Finnland.

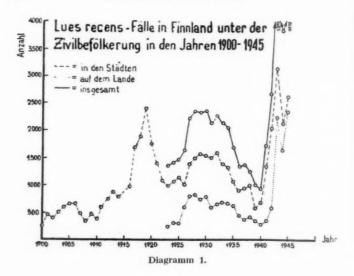
Von

BERNHARD LANDTMAN und TOIVO SALMI.

Als wir uns die Aufgabe stellten, dem Lues congenita-Problem in Finnland nachzugehen, geschah dies aus mehr denn einem Grunde. Man kann sich nämlich erstens des Eindruckes nicht erwehren, dass es sich hierbei um ein relativ versäumtes sozialmedizinisches Gebiet handelt, da bis jetzt alle Aufmerksamkeit stets und in erster Linie auf die Bekämpfung von Krankheiten von grösserer praktischer und klinischer Bedeutung gerichtet gewesen ist. Des weitern ist unser Interesse aber auch durch den Umstand geweckt worden, dass die Lues immer weiter eine von den wichtigsten Infektionskrankheiten darstellt, welche den Foetus vor der Geburt befallen können. Ausserdem hat sich durch die Kenntnisnahme, dass die Lues im Laufe der letzten Jahre in unserem Lande eine fortwährend zunehmende Ausbreitung erfahren hat, das Problem noch aktueller gestaltet.

Bei unseren Untersuchungen haben wir dieses Problem hauptsächlich vom sozial-medizinischen Gesichtspunkt aus betrachtet, wobei Fragen, die in das Gebiet der Klinik besagter Krankheit gehören, mehr in den Hintergrund haben treten müssen. Auch ist die Besprechung der Therapie vollständig beiseite gelassen worden, da sie in unserem Lande kürzlich von Enkvist behandelt worden ist.

Die Beschaffung des erforderlichen Materials war uns dadurch wesentlich erleichtert, dass in Finnland seit dem Jahre 1929 die



Pflege der kongenitalluetischen Kinder vorzugsweise im Haga-Extrakrankenheim in Helsinki zentralisiert ist. Weiterhin war uns das Patientenmaterial der Kinderklinik der Universität Helsinki zur Verfügung gestellt worden. Gewisse statistische Angaben erhielten wir von der Medizinalverwaltung sowie vom staatlichen Zentralamt für Statistik. gel

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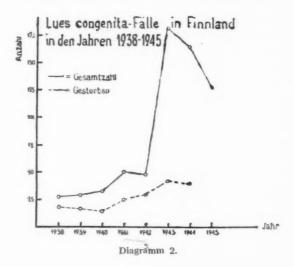
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Die Häufigkeit der Lues in Finnland.

Um für die Beurteilung des Lues congenita-Problems in Finnland den dafür erforderlichen Hintergrund zu schaffen, sind wir der Frequenzkurve sämtlicher von Stadt und Land für die Jahre 1900—1945 gemeldeter Lues recens-Fälle nachgegangen.

Aus Diagramm 1 geht hervor, dass die Frequenzkurve für Lues in Finnland zwei Zacken aufweist, die mit der Zeit der beiden Weltkriege zusammenfallen. Diese Beobachtung, dass die mit dem Kriege verknüpften Umstände den Boden für eine Ausbreitung der Lues abgeben, ist übrigens auch aus anderen Ländern gemeldet worden. Die Kurve erreicht im Jahre 1943 mit 5392 neu-



gemeldeten Fällen ihren Gipfel. Die nach diesem Zeitpunkt bemerkbare fallende Tendenz dürfte wohl zum Teil auf der allmählichen Rückkehr zu normaleren Verhältnissen beruhen, zum Teil aber auch eine Folge der Auswirkung des »Lex veneris» sein, welches im Jahre 1943 in Kraft getreten ist. Ausserdem ist aus diesem Diagramm zu ersehen, dass die Anzahl der Erkrankungen in den Städten ca. doppelt so hoch wie auf dem Lande ist.

Im Diagramm 2 finden wir die Lues congenita-Fälle für den Zeitraum 1938—45 zusammengeführt. Prozentuell schwanken diese in den einzelnen Jahren zwischen 1.8 und 4.3 % aller überhaupt gemeldeter Luesfälle. Aus dem Diagramm ergeht ebenfalls dass auch die Lues congenita-Fälle in den letzten Jahren an Anzahl in bedeutendem Masse zugenommen haben. Das Maximum wurde im Jahre 1943 mit 182 neugemeldeten Fällen erreicht. Die unterbrochene Linie zeigt den Verlauf der Mortalität an, welche in den einzelnen Jahren zwischen 21.5 und 67.9 % (Durchschnittswert 35 %) geschwankt hat. Von den Gestorbenen waren alle bis auf 3 vor Ausgang des ersten Lebensjahres gestorben. Die Sterblichkeit an dieser Krankheitsform in unserem Lande muss als sehr hoch ange-

sehen werden, da die entsprechenden Zahlen in anderen Ländern im allgemeinen nur zwischen 10—20 % schwanken.

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Man hat mit der Möglichkeit zu rechnen, dass in Wirklichkeit die Anzahl der an kongenitaler Lues gestorbenen Kinder wahrscheinlich noch um ein Beträchtliches höher ist als die obigen Ziffern dokumentieren, da in den Totenscheinen die Grundkrankheit wahrscheinlich nicht selten zu Gunsten sekundärer Komplikationen übersehen wird. Zieht man dazu die Anzahl der Aborte in Betracht, die jährlich durch die Lues verursacht werden, so dürfte der Verlust an Menschenleben, der durch diese Krankheit gezeitigt wird, zu recht ansehnlichen Ziffern ansteigen. Bei Kenntnis dieser Tatsachen scheint das Lues congenita-Problem doch ein recht weites Arbeitsfeld zu bieten.

Eigene Beobachtungen.

Unser eigenes Material enthält die Angaben über insgesamt 436 Kinder, welche in den Jahren 1920—45 auf der Universitäts-Kinderklinik in Helsinki sowie im Haga-Extrakrankenheim verpflegt worden sind. Von diesen sämtlichen Patienten starben insgesamt 186 (42.7 %).

Auf der Kinderklinik der Universität Helsinki sind von genannten Kindern 124 behandelt worden, was 0.65 % des ganzen Patienten materials der Klinik ausmacht. Zum Vergleich mag erwähnt werden, dass die von Krankenhäusern in Neapel gemeldeten entsprechenden Ziffern 10—15 % und die von Montevideo ca. 5% sind.

Im Folgenden sollen zunächst die 250 Fälle, die der Genesung zugeführt wurden, besprochen werden. Von diesen stand bei der Aufnahme reichlich die Hälfte in einem jüngeren Alter als ½ Jahr. Auffallend ist, dass 68 von diesen Kindern ausserhalb der Ehe (27.2 %) geboren waren. In 94 Fällen (37.6 %) hatten die Mütter vor der Geburt des Kindes keine antiluetische Behandlung erhalten. Der Grund dafür ist mit Ausnahme von einigen vereinzelten Fällen darin zu suchen, dass die Mütter sich ihrer Krankheit überhaupt nicht bewusst waren. Bei der Aufnahme in die Klinik hatten 162 von den Kindern noch nicht das Alter von 1 Jahr erreicht (64.8 %).

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Bemerkenswert ist die geringe Anzahl der Frühgeburten — 11.6 % — welche ungefähr der normalen Frühgeburtenfrequenz in Finnland entspricht. Eine gewisse Tendenz zu unternormalem Geburtsgewicht ist jedoch zu vermerken, indem 41.3 % der Kinder weniger als 3000 g wogen.

Von Symptomen, die die Kinder bei ihrer Aufnahme ins Krankenhaus aufwiesen, kamen am häufigsten Ausschläge verschiedenster Art vor. Solche fanden sich bei 164 Kindern (65.6 %). Der Häufigkeit nach als nächstes Symptom steht der Schnupfen (28 %). Leber- und Milzvergrösserung waren in 22 resp. 15.5 % festzustellen. Andere Symptome kamen weniger konstant vor. Symptome von Lues tarda waren selten zu konstatieren.

Von 33 Patienten — sämtliche unter 5 Jahren — haben wir vollständige Blutbilder aufgenommen. Dabei zeigte ein grosser Teil der Kinder eine recht hochgradige hypochrome Anaemie, 17 von ihnen hatten einen Hbg-Wert von weniger als 60 %. Zehn von den Kindern hatten gesteigerte Leukozytenwerte von 10000—15000/mm³. Die Differenzierung brachte keine weiteren greifbaren Unterschiede im Vergleich zu normalen Verhältnissen zu Tage als dass eine Eosinophilie — mehr als 4 % — bei 13 Kindern vorkam.

Zwecks zu untersuchen, inwieweit die kongenitale Lues Störungen in der Herzfunktion mit sich bringe, wurden von den obenerwähnten 33 Kindern Elektrokardiogramme aufgenommen. Irgendwelche pathologische Veränderungen — Arhythmien mitnet — konnten in den Elektrokardiogrammen nicht festgestellt gerechwerden.

Auffallend ist die grosse Empfänglichkeit dieser Patienten für Infektionen von nosokomialer Natur. Reichlich die Hälfte der Kinder erkrankte nämlich während ihres Hospitalaufenthaltes an verschiedenen Krankheiten, unter welchen Bronchitis, Bronchopneumonie sowie Gastroenteritis am häufigsten vorkamen.

Bei Sichtung der 186 Fälle, in denen die Krankheit zum Tode geführt hatte, erwies es sich, dass 85 von diesen Kindern ausserhalb der Ehe geboren waren (45.7 %). Es scheint also, als ob die ausserehelichen Verhältnisse Anlass zu einer schlechteren Prognose geben, wenn man sich in Erinnerung ruft, dass, wie oben erwähnt,

»bloss» 26.5 % der am Leben gebliebenen Kinder ausserhalb der Ehe geboren waren. Hierbei liesse sich möglicherweise bei den einsamen Müttern eine grössere Fahrlässigkeit in ihrer eigenen und des Kindes Pflege voraussetzen. Dieser Annahme wird dadurch noch mehr Kraft verliehen, dass von den 186 Müttern 127 (68.3 %) überhaupt keine Kenntnis von ihrer Krankheit gehabt und infolgedessen auch keine Behandlung erhalten haben.

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Von diesen 186 Kindern hatten bei der Aufnahme ins Krankenhaus 177 nicht die Vollendung des 1 Lebensjahres erreicht (95.2 %). Ca die Hälfte dieser Kinder hatte ein Geburtsgewicht, das 3000 gunterstieg (23.7 % Frühgeburten).

Im Bereich der unter Besprechung stehenden Gruppe hatien die Kinder bei der Aufnahme ins Krankenhaus häufig ganz ausgesprochene Krankheitssymptome aufzuweisen. Von den 186 Kindern hatten nämlich 169 Ausschlag (90.9 %) und 88 (47.3 %) Choryza luetica. Leber- sowie Milzvergrösserung wurden bei 81 resp. 58 Kindern (43.5 resp. 31.2 %) konstatiert. Ein Vergleich mit entsprechenden Verhältnissen bei den am Leben gebliebenen Kindern genügt um zu zeigen, dass ein direkter Zusammenhang zwischen der Intensität der Symptome und der Mortalität besteht. Einhundertfünfzig von diesen Kindern starben noch ehe sie ½ Jahr alt geworden waren. Die häufigsten Komplikationen bildeten akute Infektionen der Luftwege sowie Gastroenteritis.

Während des letzten Krieges stieg die Mortalität der kongenitalluetischen Kinder um ein Beträchtliches. Das Maximum wurde im Jahre 1943 erreicht, in welchem die Sterblichkeit unter besagtem Krankenhausmaterial 67.9 % betrug. Die Ursache für eine so hohe Mortalität ist wohl in erster Linie in den damals herrschenden Kriegszuständen zu suchen, welche es mit sich brachten, dass die Bekämpfung der Krankheit in bedeutendem Masse erschwert wurde. Als Beispiel kann angeführt werden, dass ein Mangel an Muttermilch während des Krieges sich äusserst bemerkbar machte, was sich besonders in oben relatierten Fällen schicksalsschwer auswirkte, weil ja hierbei in erster Linie Kinder unter ½jährigem Alter in Frage kamen. So konnten im Haga-Krankenhaus während des Krieges nur 10—20 % der jüngsten Kinder ausschliesslich mit Muttermilch aufgezogen werden.

Besprechung.

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Bei Betrachtung des Lues congenita-Problems in Finnland gilt es in erster Linie die Ergreifung von Massnahmen zu überlegen, die es ermöglichen würden, die im steten Steigen begriffene Frequenz dieser Erkrankungsform einzudämmen. Da die Anzahl der Fälle von kongenitaler Lues selbstverständlich in einer direkten Abhängigkeit von der Luesfrequenz bei den Erwachsenen steht, ist es offensichtlich, dass eine Verminderung der Letztern auch seine Rückwirkung auf die Häufigkeit der kongenitalen Acusserung der Krankheit haben müsste. In diesem Kampf kommt der Lex veneris sicherlich eine grosse Bedeutung zu. Dass die Auswirkung dieses Gesetzes bis jetzt noch nicht deutlich genug zu verspüren gewesen ist, muss wohl dem Umstande zugeschrieben werden, dass die Kriegsverhältnisse seine Durchführung in wesentlichem Grade erschwert haben. Einzig und allein auf diesem Wege würde es indessen nicht gelingen, die Anzahl der Erkrankungen an kongenitaler Lues effektiv einzuschränken. Unsere Untersuchungen haben ja den grossen Misstand gezeigt, dass ca die Hälfte der Mütter von Kindern mit kongenitaler Lues von ihrer eigenen Krankheit keine Kenntnis gehabt, weswegen sie auch vor der Geburt des Kindes keinerlei Behandlung erhalten haben. Diesem Missverhalten abzuhelfen müsste in erster Linie den Mütter-Beratungsstationen zukommen. Im Finnland ist es auch in ausgedehnterem Grade Brauch geworden, von den werdenden Müttern Blutproben zu nehmen, doch müsste die Kontrolle noch mehr verschärft werden, besonders was die Landbevölkerung anbetrifft. Auch müsste die Wirksamkeit der Stationen weit grössere Kreise gravider Frauen erfassen, als es bis jetzt der Fall gewesen ist. Die Verpflichtung von werdenden Müttern Blutproben zu entnehmen, müsste auch den Privatärzten sowie Hebammen auferlegt werden.

Nunmehr werden in vielen Entbindungsheimen von den auf der Station liegenden Patientinnen konsequent Blutproben entnommen, doch wird die Sachlage auch dadurch nicht verbessert, da die Luesdiagnose, wenn die Behandlung für den Foetus von effektivem Nutzen sein soll, spätestens im 4.ten—5.ten Graviditätsmonat gestellt werden muss. Der Situation könnte vielleicht etwas durch

^{8 -} Acta pædiatrica. Vol. XXXV.

Einführung einer obligatorischen Blutprobe vor der Eheschliessung abgeholfen werden. Denn so wie die Sachlage im Augenblick liegt, dürfte die von den Partnern verlangte und gegebene Versicherung, dass sie beim Eingehen der Ehe nicht an einer ansteckenden Krankheit leiden, nur eine reine Formalität darstellen. Aber auch diese obligatorische Blutprobe allein würde nicht zum erwünschten Ziel führen, da unsere Beobachtungen ja gezeigt haben, dass ca jedes dritte mit kongenitaler Lues behaftete Kind ausserhalb der Ehe geboren ist.

Eine wichtige Aufgabe im Kampf gegen die Lues kommt sicher den verschiedenen Vorbeugungsmassregeln, in erster Linie in Form von möglichst effektiver, sei es sogar schon während der Schulzeit einsetzender Aufklärungstätigkeit zu.

Was die Behandlung der kongenitalluetischen Kinder anbetrifft, so ist es offenbar, dass sie Spezialkrankenhäusern, an deren Spitze ein Pädiater steht, zufallen muss.

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Hormone Treatment of the Incompletely Descended Testicle.

By

ALFRED SUNDAL.

According to Denis Browne the position of the testicles can be divided into three categories:

1. The normal position with the testicles at the bottom of the scrotum, or in such a position that the testicle drops spontaneously when growth is completed.

The testicle which has not descended completely but has stopped somewhere on its way from the kidney region to the scrotum, from which place there will be no spontaneous descent.

3. The ectopic testicle where the testicle has left its normal course below can, ingv. ext.

This article deals with the testicle which is incompletely descended. We must remember the normal variations which are really descended testicles. These normal variations may be 1) when the testicles are not at the bottom of, but at the entrance to the scrotum. Or 2) when the testicles are of low retractability, owing to small size and to active cremaster influence so that the testicle comes over os pubis into the ingvinal pouch where it can remain for days. Or 3) the testicle can lie permanently in the ingvinal pouch. None of these types are undescended testicles. The difference between these and the incompletely descended testicles is that in the latter case, the testicle cannot be pushed manually down into the scrotum.

In the case of the incompletely descended testicle, it is sometimes possible to feel the testicle at the outer ring of can. ingv.

In cases where the testicle is in canalis or intra-abdominal, an operation is the only means of recognizing it.

The mechanism of the testicle descent is unknown. In foetal life the testicle reaches the inner ingvinal ring in the third month, but not until the 7th month does it pass through the ingvinal canal.

In the first three months, cryptorchidism is usual, about 10—15%, but in the course of the first year descent is so usual that at the age of one year, one finds incomplete descent in 1—3%. The testicle can also descend later in childhood but the percentages vary greatly. W. W. Johnson found that in 50% the descent came between the ages of 5 and 17, while Campbell states that spontaneous descent occurs only for 5% after the age of one year. The reason for imperfect descent is unknown. In some instances, anatomical circumstances can explain the condition, and in others predispose for retention, but anatomical circumstances can not explain all cases. One must presume that the pituitar-gonadotrope hormones play a part in many cases.

SCHAPIRO (1930) and ENGLE (1931) have shown that injections of hormones from the anterior lobe of the hypophysis, and hormones from the urine in pregnancy, caused increased growth of the testicles. Turgescence and swelling ensued and the retarded testicles descended more or less. The enlargement of the testicles observed after hormone treatment, is due to the increase in the interstitial tissue.

The importance of imperfect descent of the testicle lies first of all in that retarded testicles very often prove to be sub-normally developed, occasionally they are highly atrophied. The reason for this can be primarily atrophied testicles or often a thermal injury. It is well known that a testicle which is transplanted to the abdomen in puberty loses spermatogenesis, which returns when the testicle is replaced in the scrotum. The scrotum has been called the radiator of the testicles. The genuine testicle retention has another significance in that it can be combined with rupture since proc. vaginalis peritonei is not obliterated and incarceration can occur in such ruptures. In cases of bilateral retention, there is danger of sterility, especially if the retention is intra-abdominal

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and persists during and after puberty. Incomplete testicle descent can also cause local symptoms such as pain. In boys of school age a faulty development of this kind can give rise to psychic depression and a feeling of inferiority, especially when the fault has been discovered by ruthless companions. It should also be borne in mind that neoplasm occurs much oftener in retained than in descended testicles.

Taking all these things into consideration it seems to me that it is best to bring an incompletely descended testicle into place as soon as it can be done without injury. Formerly the only treatment was surgical and where the retention is complicated by hernia or hydrocele, the operative treatment is the only right one. If, however, it is a case of incomplete descent, without established complications of a pathologic anatomic nature, hormone treatment should be given. This treatment has had and still has, its enthusiastic advocates and its equally energetic opponents. Thompson and Heckel by grouping 281 bilateral and unilateral cases of testicle retention, observed descent in 61 % after hormone treatment. By operating on eleven of the patients who did not respond to the hormone cure, in every case, pathological anatomical changes were found which prevented descent: short fibrous ligaments which fastened testis and the spermatic cord, and an abnormal direction of proc. vaginalis. In genuine cryptorchidism Thompson and HECKEL got descent in only 27 % and surgical treatment was necessary in 3/4 of the cases. They point out however, that hormone treatment is not without value, nevertheless, because after the treatment, the organs are larger and the testicles could be brought into place in the scrotum, by operation, without injury to the veins.

There has been much dissension as to when the treatment of incompletely descended testicles should be made. This is reasonable, considering the very different records for the possibility of spontaneous descent later in the child's life. As stated above, these records of spontaneous descent vary from 5 to 50 %. A glance through various publications gives one the impression that these widely varying figures are due to the different interpretation of the term *testicle retention* so that elevated testicles which

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Name	Position of the Testicles.	sticles.	Hormone dose	Domonica
Age	Before Treatment	After Treatment	Treatment	remarks
I. Aa. H. 7—3/12 yrs	Left testicle descended. Right Right testicle loosened, can 10×200 mouse testicle stationary at entrance to easily be pressed down into units (M.U.) in scrotum	rt testicle loosened, can y be pressed down into	can 10×200 mouse into units (M.U.) in 30 days	In this case Hormone treat- ment probably unnecessary
II. Chr. H. 7-8/12 yrs	L. testicle descended. R. testicle R. testicle slightly above enjust palpable in can. ingvfixed trance to scrotum, can be pressed down. One month later: descended still more	R. testicle slightly above en- trance to scrotum, can be pressed down. One month later: descended still more	15×200 M.U. 60 days	
III. P. K. 10—10/12 yrs	1. P. K. R. testicle descended. L. testicle I. testicle can be pressed down 10—10/12 yrs feels small and atrophically fixed to entrance to scrotum after 5 in can. Ingv. nore, descended to beginning of scrotum and can be pressed right down	L. testicle can be pressed down to entrance to scrotum after 5 injections more, descended to beginning of scrotum and can be pressed right down	10×250 M.U. 40 days	Rise of temp. to 39° C the first two injections. No reaction later
IV. J. K. 11-1/12 yrs	Small genitalia. L. testicle desc. Complete descent of R. test. ended. R. testicle can be felt just after 3 injections outside can, ingv; cannot be drawn	plete descent of R. test.	3×200 M.U. 10 days	
V. P. S. 11—2/12 yrs	L. testicle descended. R. test.L. testicle at the entrance to somewhat below the subcutaneous scrotum, can be drawn down groin ring. Fixed.	esticle at the entrance to tum, can be drawn down	10×200 M.U. 40 days	
VI. L. S. 6—8/12 yrs	L. testicle descended. Operated for R. test. larger, looser and deschernia ingv. dextr. and retentio ended to entrance to scrotum, test. R. test. feels like a coffeecan be pressed still further bean, stationary in lower edge of down the scar after operation	est. larger, looser and desc- ed to entrance to scrotum, be pressed still fürther n	10×200 M.U. 20 days	
VII. E. E. 8 yrs	R. test. descended. Operated at Complete descent of L. test. the age of 6 for left-side groin rupture and test, retention. L. test feels small and fixed in the lower part of scar.	plete descent of L. test.	10×200 M.U. in the course of 20 days	

7—6/12 yrs	Both test, paipable at annulus Considerable growth of the ingv. subcutan. Can not be pressed genitals. Complete descent of down	Considerable growth of the genitals. Complete descent of both test.	8× 200 M.U. Enlargement 16 days receded after	Enfargement of penis receded after one month
IX. B. A. 6-6/12 yrs	Both test. fixed just below the R. test. completely bescended. L. test. descended to entrance to scrotum	R. test. completely bescended. L. test. descended to entrance to scrotum	10×200 M.U. 40 days	
X. K. E. 12—10/12 yrs	Dystrophia adiposo-genitalis. Loss of weight 6.2 kg Height 154 cm (+ 7 cm). Weight: completely descended 64.2 kg (+ 20 kg) L. test. desc- ended R. test. fixed just at annulus ingv. subcutan	Loss of weight 6.2 kg. R. test. completely descended	10×200 M.U. 70 days	
XI. R. T. 611/12 yrs	Small genitalia. Testicles not palp- Some growth of genitalia but testicles not palpable. Operation immediately after last injection	Some growth of genitalia but testicles not palpable. Opera- tion immediately after last injection	10×250 M.U. 24 days	Operation: L. test. just inside the subcutan. groin ring. Vas. deferens thick, looped. Tension put on test. R. test. not visible. Hernia on r. side
XII. H. K. 6-6/12 yrs	Cerebral haemorrhage at birth. L. test. can be felt after 5 Somewhat imbecile. Test. not injections. After 8 injections, palpable into the scrotum. After 10 inject. in all, no more change. R. test. not palpable	at birth. L. test. can be felt after 5 Test. not injections. After 8 injections, l. test. can be pressed down into the scrotum. After 10 inject. in all, no more change. R. test. not palpable	10×250 M.U. 26 days	Operation on the retained R. test. not performed
XIII. J. B. 6 yrs	Debil. L. test. descended. R. test No descent of R. test. Scanty not palpable growth of the genitalia Operation	No descent of R. test. Scanty growth of the genitalia Opera- tion	10×200 M.U. 40 days	Operation: R. test. not palpable in or just inside can. ingv.
XIV. O. R. 107/12 yrs	Adipositas, Glaucoma cong. L. No descent of R. test. No test. descended. R. test. not growth of the genitals. Operapalpable tion just after last injection	L. No descent of R. test. No not growth of the genitals. Operation just after last injection	10×200 M.U. 38 days	Operation: The retained R. test. lay just behind the subcutan. groin ring and could easily be drawn down into the scrotum

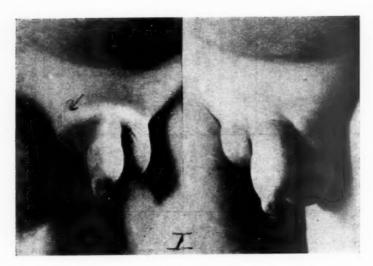


Fig. 1.

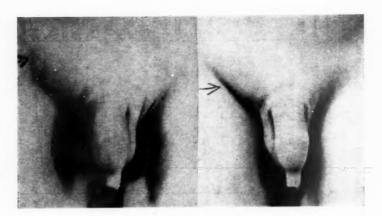


Fig. 2.

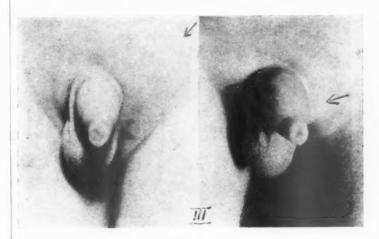


Fig. 3.

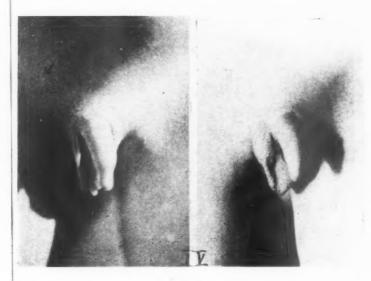


Fig. 4.

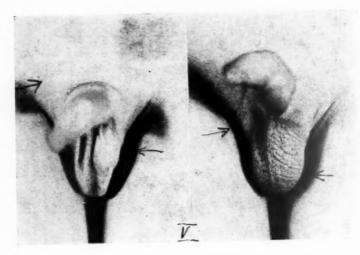


Fig. 5.

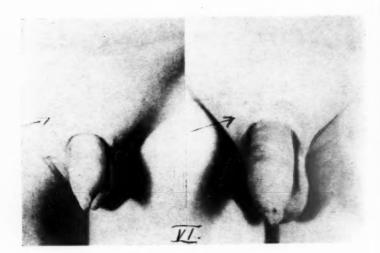


Fig. 6.

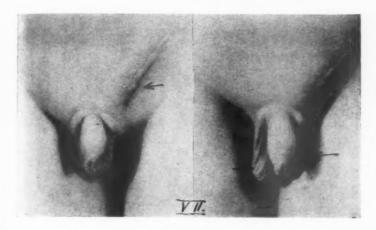


Fig. 7.

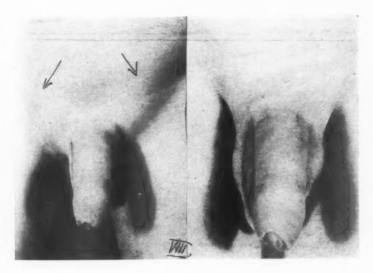


Fig. 8.

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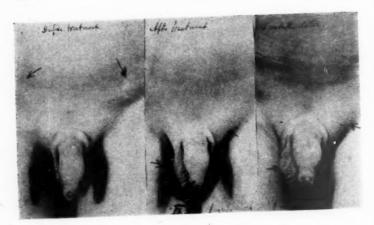


Fig. 9.

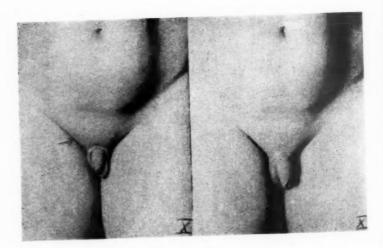


Fig. 10.

are a normal variation of descended testicle, are counted as retained testicles. While one would naturally wait as long as possible before operating, to see whether spontaneous descent comes with puberty, one can very well begin earlier with the less radical hormone treatment, considering the statements which have been made above about the handicap of retained testicles. It seems one should agree with Campbell, that if without injury one can bring a retained testicle in position, it is better to do it at the age of 7—8 years rather than to wait until the age of 12—17; even if there is a possibility that some testicles which showed retention at 8, would perhaps descend spontaneously, later.

My own records include 14 patients between the ages of 6 and 13 years, with incomplete descent of the testicles. Since there were no indications to advocate operative treatment, hormone cures were given, with Physex Leo, a chorion hormone, made from urine from gravid women where the gonadial hormone is standardized on the mouse according to the lutein action. There were given as a rule, intra-gluteal injections, every third or fourth day, each time 200 mouse units (M.U.)-sometimes, 250 M.U. ¹

As a rule, after the first 3 or four injections there was growth of the penis and scrotum and of the descended testicle in those cases where there had been retention on one side only. Where the retained testicle could be felt and was fixed, it increased after a few injections and became more mobile. In the course of the follow-) ing injections descent took place, usually before the 10th injection. In my cases, the growth of genitilia caused by the hormone treatment has gone partially or completely back to normal in the course of 3 or 4 weeks after the last injection. BIGLER, HARDY and Scott, however, have reported lasting enlargement of penis so that one would hesitate to give hormone treatment before the eighth year. In my cases I saw no side effects except in one patient who reacted with a rise of temperature (39°C) after the first two injections. In the meantime there have been reported accompanying reactions in the form of severe headache, weakness and gastrointestinal symptoms.

Thus: Out of 14 patients 10 had unilateral retention, 4, bilateral.

¹ Ove M U. is about 10 rat units (R.U).

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Fig. 11.

In the case of the 18 retained testicles, hormone treatment brought about the satisfactory descent of 13. In 12 of these 13 cases, the testicle was palpable before treatment, cryptorchid in one. Four patients with 6 cryptorchid testicles in all, showed descent of one testicle after hormone treatment, no sign of descent in the other 5. An operation was made on 4 of these testicles immediately after the cure: 2 of the testicles were found lying just at the subcutaneous groin ring and could easily be drawn down into the scrotum, while the other two testicles could not be found at all during the operation.

From my experiences, the best results are obtained with 10

injections of 200 M.U. If this fails to give results, an operation should be performed and the operation is facilitated if it is made the first week after the last injection since the genitilia are enlarged and the tissue around the testicles and testicle veins is often looser so that the testicle can be drawn down more easily.

Hormone treatment gives the best results in cases of incompletely descended testicles, and where the retained testicle can be felt at the subcutaneous groin ring. In the case of cryptorchidism, with palpable testicle lying intra-abdominally or in can. ingvinal, it is not known, namely, whether there are complications with hernia, hydrocele, atrophied testicle fixed by tight veins etc, which if the abnormality were known, would indicate surgical treatment. But even if such pathological anatomic complications are present, a hormone cure will not spoil the result of surgical treatment, — quite to the contrary.

The surgical treatment of testicle retention gives very different results in some statistics. Kraetsch gives good results in 37 %, poor in 63 %. American statistics (Counceller, Walters and Thiessen, Eisenstaedt, Appel and Fraenkel) find good results from surgical treatment in 87 to 93 %. The correct treatment, therefore, appears to be, hormone injections where there is incomplete descension of the testicle without evident pathologic anatomic complications, immediately followed by operative treatment when the hormone cure fails to give the desired results.

Summary.

Incomplete descent of the testicle should be treated in childhood, preferably from the age of eight upwards. Injections of gonadotrope hormones should be given these patients if the testicle retention is not accompanied by evident pathologic anatomic complications, such as hernia and hydrocele which indicate surgical treatment. Hormone treatment gives very good results with testicle retention where the testicle can be felt in or below the subcutaneous groin ring. The result may be less satisfactory in cases of cryptorchidism as the retention is often complicated by hernia or atrophied testicle. If the hormone cure fails, immediate operation is advised,



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18.

Sella turcica in obesity in children.

By

HANS-OLOF MOSSBERG.

During the last twenty years the question of the size of the sella turcica and its relation to that of the hypophysis has been subject to much discussion within Roentgenological and Endocrinological circles. In this connection, some authors have also touched upon the condition of the sella turcica in obesity. The object of this paper is to further illustrate these conditions on the basis of a larger number of cases of adiposity. First, a few words about the method of determining the size of the sella profile and its normal limit values.

The method used is the mm²-method described by Haas (1925). The measuring is done by copying the outline of the sella on a mm-squared paper and the number of mm² is added up. As upper limit — representing the entrance of the sella — is chosen the connecting line between the lowest point of the tuberculum curve and the inner point of the Dorsum tip. Furthermore the surface is calculated on the *median* sella profile according to BOKELMANN (1934).

Many authors have followed the method of Haas giving the normal values for the size of the sella turcica in children. The normal curves show rather important divergencies but generally the case-material has been, for obvious reasons, small (100—200 cases). Haas himself (186 cases), Kovács (650 cases) and to a certain extent Sartorius (100 cases) hold an intermediate position. The data as to the normal distribution is divergent, and the limit

^{9 -} Acta pædiatrica. Vol. XXXV.

Table 1.

Normal values of the sella turcica in own investigation.

Year group	No. cases	Mean (M) mm²	σ	М±2 б	Successive mean value of M±2 o
0-1	18	21.7	15.5	52.7 —9.3	
1-2	61	38.0	5.7	49.4 26.6	53.1 18.
3-4	59	47.9	4.6	57.1 38.7	56.8 36.
56	52	54.4	4.7	63.8 45.0	63.1 44.
7-8	51	58.5	5.0	68.5 48.5	68.4 47.
9—10	58	60.2	6.3	72.8 47.6	72.1 48.
11-12	45	61.9	6.5	74.9 48.9	78.7 48.
13-14	40	68.7	9.9	88.5 48.9	86.7 50.
15-16	46	75.5	10.6	96.7 54.3	100.5 51.
17-18	42	84.2	16.1	116.4 52.0	108.2 55.
1920	45	86.1	12.7	111.5 60.7	114.4 56.
2122	47	85.3	15.0	115.3 55.3	114.1 57.
23-24	42	86.5	14.5	115.5 57.5	114.9 57.
25-26	43	87.4	13.2	113.8 61.0	112.9 59.
27-28	45	85.1	12.2	109.5 60.7	109.6 63.9
2930	42	87.8	8.9	105.6 70.0	-

values reported have not been calculated with regard to statistical methods.

In order to obtain a normal case-material of my own according to Haas and Bokelmann, where statistically positive limit values could be calculated, commotio cases, with at least 20 cases in each year group, were chosen as a basis. Before the age of about 10 years the weight could be controlled. It was not allowed to exceed $\pm 2\,\sigma$ according to the weight-length tables issued by Broman, Dahlberg & Lichtenstein. The result appears in fig. 1 as compared with the values of the literature. The average values show good conformity with the values of Haas and Kovács. As limit values have been chosen $\pm 2\,\sigma$ (Tab. 1). In normally distributed case-material such as 1 am using at present, only 5 values out of 100 fall outside these limits, which does not justify a wider determination of the border-lines. If a value surpasses these limits the possibility thus is 95 out of 100 that a pathological value is present.

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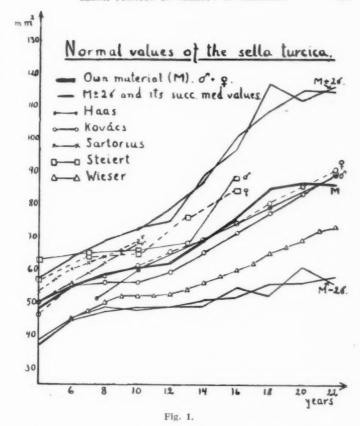
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When determining the profile picture of the sella turcica by X-rays the idea is to get a measure of the size of the hypophysis. The question of a possible connection has been much discussed and opinions have been divergent. The assumption of a correlation has been based on the circumstance that the average normal values of the sella size and of the hypophyseos weight in different ages determined separately follow each other. Simultaneous investigations on the sella size in the X-ray picture and the volume of the respective hypophysis are made by BOKELMANN (1934), KOVÁCS

Table 2.

Sella turcica and corresponding hypophysis in own investigation.

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Case	Age	Volume	Surface	Hypoph
No.	Years	hypoph. mm³	sella mm²	Sella
1	1/12	35.3	10	3.53
2	1/12	50.3	15	3.35
3	1 1/2/12	72.2	14	5.16
4	1 1/2/12	40.7	13	3.13
5	2 1/2/12	50.0	15	3.33
6	3/12	78.6	19	4.14
7	3/12	46.0	14	3.29
8	4/12	68.3	22	3.10
9	8/12	81.6	27	3.92
10	9/12	86.1	23	3.74
11	10/12	80.3	25	3.21
12	1	77.4	24	3.23
13	1 1/12	123.8	37	3.35
14	1 5/12	85.9	29	2.96
15	1 10/12	97.1	32	3.03
16	2 6/12	97.0	32	3.03
17	2 7/12	135.9	38	3.58
18	2 8/12	95.1	32	2.97
19	4 9/12	136.4	46	2.97
20	7 8/12	176.5	66	2.67
21	10 10/12	159.2	50	3.18
22	15	237.0	68	3.49

(1934) and Ottaviani (1938). The very thorough investigation of the first mentioned author showed that there was a definite connection only in the cases of the very small hypophysis. In the work of Ottaviani no connection could be shown. Both the investigations concerned adults only. Kovács also considered that there was a certain connection, but was of the opinion — rightly so — that his series (12 cases) was too small to allow of positive conclusions. Four or five of his cases were children. One may a priori expect a larger conformity in adolescence than in maturity. In regard to adults endocrine disturbances and diseases have had time to influence the size of the hypophysis.

The author is engaged in a similar examination but here also

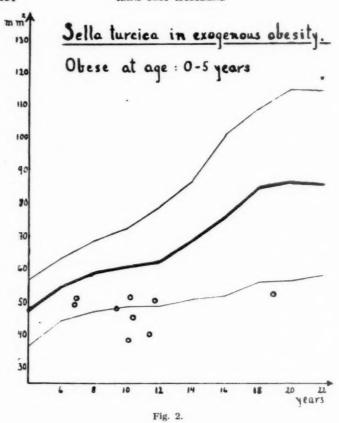
the data is as yet too small (22 cases) and does not allow of any positive conclusions (Tab. 2). The values lend a certain support to the fact that a connection may exist but only a continued investigation can give a definite verdict.

Another question is whether a small hypophysis also has a function insufficient for the need of the body, and a large hypophysis a corresponding hyperfunction. Haas (1925) was of the opinion that such a parallel existed. That this, however, is not always the case we learn from the clinic of the pituitary tumors and cysts.

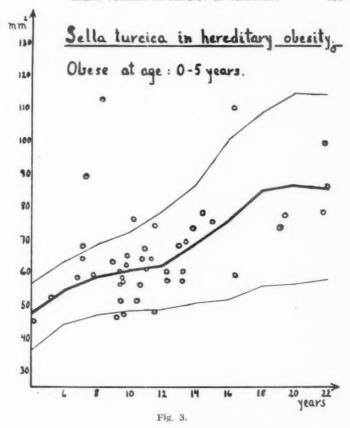
The size of the sella profile in obesity is remarkably little discussed in medical literature and only on the basis of a small number of cases. Haas (1925) and Steiert (1928) consider that there does not exist any characteristic sella picture. Haas says, however, that there are often large sellas in adiposity, but neither he nor Steiert have classified the obesity cases. Neither has Rony (1932). He reports a series of 24 children where 1 sella was *extremely small*, 3 *small* and 2 *rather large and deep*. Reinert (1926/27) relates a pathologically small sella (30 mm²) in a 10 years old child with adiposo-genital dystrophy. The literature indicates as typical in this disease, m. Fröhlich, a large sella with enlarged sella entrance (Erdheim & Schüller, cit. Assmann). Out of Haas' 7 cases of this disease in children and adults only one case showed this typical picture, 4 an enlarged sella and 2 a normal one. Steiert describes 2 cases of children with large sellas.

The present material consists of obese children treated at Kron-prinsessan Lovisa's Children's Hospital of Stockholm before 1944 and reexamined later on. In 136 cases X-rays of the sella have been made. The profile surface of the sella turcica has been determined with exactly the same method as has the normal data mentioned above. The obesity cases have been classified as follows:

- I. Exogenous
- II. Endogenous
 - 1. Constitutional
 - Endocrine (Fröhlich-type, Adiposo-gigantismus, Nanismus)
 - 3. Cerebral

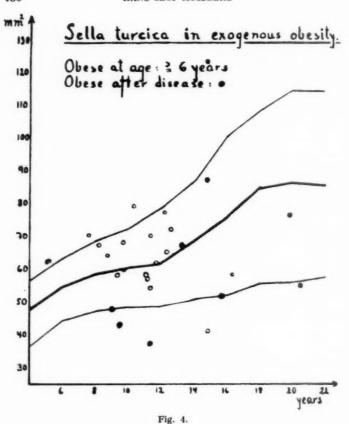


In every attempt to classify obesity one must realize that a schedule only gives certain main types and that between these numerous transitions and combinations are to be found. One may distinguish between two large essential groups, the exogenous and the endogenous. The endogenous group is divided into the constitutional and the endocrine subdivisions between which there is no defined limit. Both may ultimately have an endocrine pathogenesis although, with our present methods of examination, this is not possible to establish in the majority of the hereditary cases.



Therefore, in this classification only cases with marked adiposogenital dystrophy (Fröhlich-type), giants and dwarfs, have been referred to the endocrine group. Finally, as a special group comes the cerebral obesity which appears in immediate association with definite or probable cerebral disease.

In a diagram showing the size of the profile surface of the sella turcica in obesity the time was taken into consideration when, according to anamnestic reports, the child started growing fat. It is found that the usual age at the onset of obesity is in

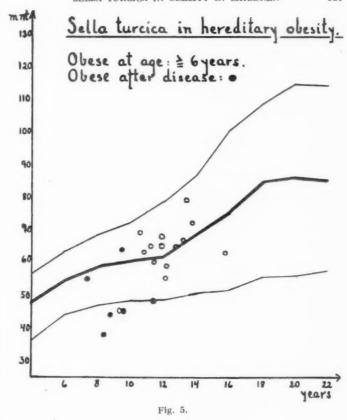


the period 0—3 and 8—11 years. Therefore, the cases up to 5 years have been referred to one group and the cases after 5 years to another. Furthermore, all cases, in which the mother reports the child to have grown fat immediately after a disease, have been specially marked in the diagrams. Diseases denoted as affecting this condition have been exceedingly varied such as otitis, pleuritis, perforated appendicitis, polyarthritis, scarlatina, abrasio, tonsillectomy etc.

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In fig. 2 we see exogenous cases which have grown fat during the first 5 years of life. The values of the sella turcica in these cases all are close to the lower normal limit. In fig. 3 we find corresponding ages for the constitutional obesity. The values are here mostly gathered round the average value of the normal reaching both up and down towards the limit values. Here are also some values which are extremely high. The corresponding groups in the age of 6 years and more are seen in figs. 4 and 5. The former shows the exogenous cases, the latter the constitutional ones. No

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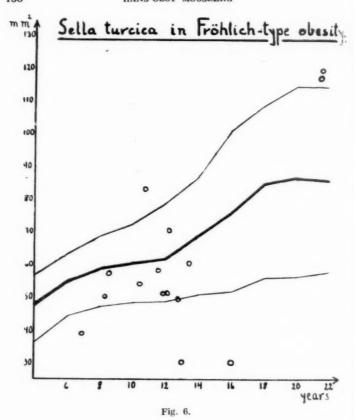
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certain difference can be shown between them. In both figures the filled-in circles mark cases which have grown fat after a disease. Their sella turcica is in 10 cases out of 12 below the average value and 9 of these are on or under the lower limit of the normal. In fig. 6 the sella sizes of the Fröhlich-resembling cases are marked. The values show a marked tendency to be low, 11 out of 15 cases fall under the average value and 3 out of the 11 are pathologically small. The giants and the dwarfs, as well as the cerebral cases, do not show any tendency in one direction or the other, but here

also we find the same condition; cases which have grown fat after a disease have a low value (4 out of 5 cases).

Especially noteworthy in the above shown diagrams is the common occurrence of small sellas in obesity in children. Small sellas in adults, as Bokelmann has shown, very often contain small hypophysis. In children the relation hypophysis-sella turcica is probably still more certain. The possibility, therefore, that the obesity in these cases of adiposity in children is due to an insufficient pituitary function has a certain support. The exogenous cases having grown fat early, and cases which have grown fat in connection with a disease, such cases all having a small sella, may have this pituitary insufficence as a cause. A theory towards the explanation of this mechanism is that the function of the hypophysis as metabolic regulating organ is insufficent to respond to the body's augmented demands of raised oxidation on increased exogenous factors such as greater intake of food or lying in bed. The small hypophysis and sella in these cases is probably constitutionally determined. Also the Fröhlich-cases with the marked features of the adiposo-genital dystrophy, which in children often does not have the same serious aspect as in adults, have this tendency to low values of the sella. In the diagrams shown the pathologically high values of the sella are not found in any special group of obesity and therefore evade closer etiological discussion. It is my hope to be able to return to these questions with a larger case-material and in a wider connection.

Summary.

In the present paper the literature of the X-ray picture of the sella turcica is surveyed with special reference to the method of determining its size. The normal size of the sella in children is shown in an own normal case-material where the normal limits are statistically calculated. The correlation between the size of the hypophysis and the sella turcica is illustrated. After a short review of the literature concerning the sella in obese children and a classification of the obesity, there follows a description of the relation of the sella turcica to the different types of obesity. Cases

of exogenous obesity appearing during the first years of life, and cases of obesity following various diseases, generally show small values of the sella turcica. A theory of the pituitary connection is advanced.

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Three cases of congenital laryngostenosis with different etiologies.

By

B. HAMNE.

1. Case of goitre with mainly retrotracheal location. Congenital goitre is not always easy to diagnose. By exercising pressure on the large cervical veins and causing compressure of trachea resulting in pulmonary hyperaemia spreading up to the neck and head, the thyroid enlargement may lead to a general swelling of the soft tissues of the neck, whereby the thyroidea itself becomes impalpable. As thyroidea at birth is not only situated higher than later in life, but also normally stretches behind trachea (occasionally behind oesophagus) and the main part of the goitre may be retrotracheal, a profile X-ray examination of the neck may in these cases have to be resorted to in order to elucidate the nature of the disturbance. In this particular case the retrotracheal goitre caused a bend to form at right angles between the larynx and the trachea. When attempts at breast-feeding were made, the child's head was bent somewhat forward with resulting danger of asphyxia.

Treatment. A cushion is placed under the child's shoulders to stretch the organs of the neck. Food is administered with a probe to begin with. Congenital goitre responds to treatment with iodine, but regarding the dosage very confusing indications are found in the literature dealing with this subject. The author, who has worked in a goitreinfested district for the past $3\frac{1}{2}$ years and witnessed rapid improvement in congenital goitre cases through

daily administration of 5 mg KJ without any side actions whatsoever, supports the opinion of those who hold that the iodine tolerance in infants suffering from goitre is higher than in adult patients. It is conceivable, however, that the most suitable dosage may differ in different parts of the world.

2. Case of congenital, intratracheal goitre. Exit 9 h. after birth. While referring the reader to O. Hultén in Nord. Med. Tidskrift 1937: 2047—2049 for the etiology of intratracheal goitre, the author wishes to stress, in quoting this case, that due attention should be paid to the possibility of intratracheal goitre being congenital when discussing the etiology of this complaint.

3. Congenital stenosis of the trachea of a nature previously unknown. A full-term male infant exhibits pronounced stridulous breathing from birth until it dies at the age of 7½ months from broncho-pneumonia. The section reveals an hour-glass shaped circular stenosis in subglottis approximately at the level of the lower edge of the cricoid cartilage (lumen about the size of a knitting-needle, impassable to a button-probe). The stenosis is due to the mucous membrane being highly thickened and the hyperplasia mainly to closely set and enlarged lobuli of the mucous glands. Above and below the stenosis the mucous membrane is quite thin and contains relatively few glands, thus being strongly contrasted to the hyperplastic area. — This kind of congenital stenosis of the larynx does not seem to have been mentioned before in literature relating to this subject.

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The author has previously written on congenital goitre in Nord. Med. Tidskrift 1934: 1562—1566, and case No. 3 of the present communication, dealing with laryngostenosis of a nature previously unknown, has already been published in ActaMedica Scandinavica, Suppl. CLXX, 1946 (in honour of Prof. Bergmark).

20.

Follow-up Examinations of Cases of Poliomyelitis.

By

A. ARVOLA.

During the year 1946, the writer has performed follow-up examinations on patients treated for poliomyelitis at the Hospital for Communicable Diseases in Helsinki during the years 1937—42. Thus the follow-up examinations took place $3\frac{1}{2}$ — $8\frac{1}{2}$ years after the onset of the disease. During the years mentioned, a total of 185 cases diagnosed as poliomyelitis ant. ac. were treated at the hospital. Of these 117 were true cases of paresis. The mortality in this latter group was 19 cases (or 16.8 %), all in the acute stage of the disease. Three of the surviving patients later died of some other ailment.

At the time of the follow-up examination 95 of these remaining paresis patients were still alive. Of these 73 submitted to examination, and a further 17 gave satisfactory replies to the questionnaire sent them. The case material for this investigation thus includes 90 cases.

Degree of invalidism.

Of these cases, 15 (or 17 %) were found in the follow-up examination to have recovered completely, with no functional or anatomic defects occasioned by poliomyelitis.

The degree of invalidism has been determined in percents and using the ASPLUND and BERGMAN classifications (cf. Tabel 1).

I found slight defects causing no invalidism in 24 % of all patients, and only slight invalidism in a further 18 %, which makes a total of nearly 60 % nearly of completely cured.

Table 1. Degree of invalidism noted in control examination of paresis cases at different ages. (Numbers in parentheses give the percentage of cases from the total number of cases in the same age group.)

				Invalidity	dity				
Age	% 0	/II – < 10 %	II + II +	I, II—, II+ 0—30 %	$\begin{array}{c c} III - & III + \\ 30-50 \% & 50-70 \% & 70-90 \% \\ \hline \end{array}$	50-70 %	VI 70—90 %	V 90—100%	Total
Preschool children	6	70	10	19 (76 %)	89	-	61	Brown.	25 (100 %)
School children 7-14 years	2	4	4	13 (62 %)	4	7	67		21 (100 %)
Adults > 15 years	-	13	7	21 (48 %)	7	7	9	8	44 (100 %)
Total	15	22	16	53	14	10	10	8	06
	(% 21)	(17 %) (24 %) (18 %)	(18 %)	(% 69)	(16 %)	(11 %)	(11 %) (11 %) (3 %)	(3 %)	(100 %)

Table 11. Different types of pareses at the acute stage of the disease.

			Cranial n	Cranial nerves not affected	affected			Cranial	Cranial nerves affected	ffected	
	Lin	Limited Pareses	ses	Extensive	Extensive combined pareses	d pareses		spinal	Cuinol		Total
Age	of lower limbs only	of lower of upper of lower limbs limbs only limbs	fupper of lower limbs or upper only	of several limbs	of several limbs + trunk	Total	Total	chord not affected	chord	Total	of
Preschool children < 7 years	16	4	20 (83 %)	4	1	4 (17 %)	4 24 (17 %) (100 %)	24	1	8	27
School children 714 years	oc	8	11 (55 %)	1	5	9 (45 %)	9 20 (45 %) (100 %)	9	0.000	9	26
Adults > 15 years	11	9	(30 %)	21	<u>∞</u>	39 (70 %)	56 (100 %)		ac	oc	64
Total	35	13	18	32	20	52	100	æ	10	17	117

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 ${\it Table~III}$ Improvement of paresis under hospital care (during 1—2 months).

		Degree o	of improvement	t	
Age group	Slight	Fair	Very considerable	unknown	Total
Preschool children (< 7 years)	1	8	14	2	25
School children (7-14 years)	3	11	6	1	21
Adults (15—19 years)	7	9	3	_	19
Adults (20—29 years)	10	6	_	_	16
Adults (>30 years)	7	2	_	_	9
Total	28	36	23	3	90

A moderate degree of invalidism persisted in 27 % of all cases, and severe invalidism in 14 %, of which latter 3 were total invalids.

On the basis of the case histories I was able to ascertain that children generally suffer from a less severe form of the disease than adults, paresis in children being generally restricted to a smaller area, even in the initial stages, though severe cases also do occur (Table 2). Almost all of the children recovered completely, the majority of them being under 7 y. (the age at onset of the disease is meant here as in all later references).

The follow-up examination showed that 76 % of the children under 7 y. 62 % of those at school age, and 48 % of the patients aged 15 years or over had recovered completely or nearly so. Thus the younger the patient, the better the prognosis.

Even while yet under hospital treatment, that is to say during the course of the first 1—2 months, it was observed that the younger the patient was, the better the recovery. Even during this first period 3 children (2 of them under 7 y.) recovered completely (Table 3).

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Improvement after leaving the hospital (after acute stage) in different invalidism groups of children and adults. Table IV

Invalidism	Age		Inva	llidity at	the contr	Invalidity at the control examination	ition		Impr	Improved	T	Total
at the end or acute stage	group	% 0	II	11 + 11 10—30% 30-	30—50%	1 — III + -50% 50—70% 70-		V V V < 15 y	<15 y	>15 y	>15y<15y	>15 y
1	<15 y	က	i	i	1	i	1	i	1	1	89	1
%0-	> 15 y		-				-		i	-	1	1
II	< 15 y	90	4	-	Fabruar	1	. i	1	00		12	1
< 10 %	>15 y	1	61	i	1	1	1	i	i	-	1	ಣ
+11	<15 y	1	က	69	-	i	i	1	4	1	7	i
10-30 %	> 15 y	1	11	7	1	i	1	1	l	11	i	13
—III	<15 y	c1	1	4	1	1	i	1		1	90	1
3050 %	> 15 y	1	1	4	1	1	I	1	1	¥	i	10
III+	< 15 y		1	61	4	61	1	1	7	1	6	I
20-70 %	> 15 y		1	-	ଧ	2	1	ı	1	3	1	20
IV	<15 y	1	i	I	ล	1	4	i	8	1	7	1
% 06-02	> 15 y				4	2	4	i	1	6	I	13
^	<15 y	and the same of th	1	Bressess	r-manu	and and a	-	i	1	i	1	1
90-100 %	>15 y	1	i	1	1	1	5	3	1	2	1	20
Total		15	22	16	14	10	10	es	29	30	46	44
									100 001	100 00/ 100 00/		

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Table V Improvement of paresis in individual muscles of the limbs (numbers in percentage)

At the end of acute stage		At the	control	exam	ination	1
	Cu	red	Bette	-		lren + lults
Severity of individual muscle paresis	children	Adults	children	Adults	cured	Better or cured
Total paresis (no muscular contraction observed)	-	_	213	51		17
 Particularly severe paresis (so weak as to be unable to move limb though muscular contraction noted) 	68.0	-	12.5*	Эв	-	11
3. Severe paresis (Limbs move but weakly)	14		64	31	7	47
4. Moderate paresis (Limbs move fairly strongly)	15	9	63	44	13	54
5. Slight paresis (only slight muscular incapacity)	88	62	88	62	74	74

1 result of cure: particularly severe paresis.

Some of the slight cases and a few of the moderate ones also recovered completely after leaving the hospital (Table 4). In general recovery progressed further in children than in adults after discharge from the hospital, only the severe cases making an exception to this rule. Among the adult patients, on the other hand, only one case, of slight paresis, has made a complete recovery, the rest showing at best only relative improvement.

It may thus be stated that the prognosis for the disease in all its stages is better for children than for adults.

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Table VI
Time of cure in cases of completely cured paresis
(Number of patients, adults in parentheses)

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Paresis at the end	Tim	e of cure f	rom incep	tion of dis	ease
of acute stage	< 3 months	3-6 months	½—1 years	1—2 years	< 2 years
1. Total paresis					
2. Particularly severe paresis					
3. Severe paresis				1	1
4. Moderate paresis			1	1	
5. Slight paresis	4	1			(1)
6. Cranial nerve	4	1	1		(1)

Cranial nerve paresis.

The prognosis for cranial nerve paresis seems usually to be favourable (Table 6). Of a total of 9 cases 7 recovered completely, most of them in two or three months. Two have remained very slightly paretic. The cranial nerve cases include 2 adults, of which one recovered completely while the other remained very slightly paretic.

Paresis of extremities.

I have classified pareses of the extremities according to their severity, i.e. the loss of muscular function, in order to ascertain what recovery was made by different degrees of paresis (Table 5). I have thus compared developments in 435 muscles or groups of muscles, of 70 patients, the results being given in percentage. Comparing their condition at the end of the acute stage, i.e. 1-2 mos. after onset, and at the time of the follow-up examination I was able to ascertain that:

 in those cases in which some muscle or muscle group showed so little function at the end of the acute stage as to be unable to move the limb, or if the muscle was entirely paralyzed, this condition had up to the follow-up examination generally remained unchanged or very slightly improved. Nor was the improvement in the case of children appreciably greater than for adults.

- 2) muscle paresis allowing the patient to move the affected limb weekly 1—2 mos. after commencement of the disease showed considerably more improvement: Such muscles showed improvement in 64 % of the children and 31 % of the adults, and returned to normal in 14 % of the children, though in none of the adults.
- 3) muscles easily capable of moving the limb, though noticeably weakened, improved in over half of all cases (in 63 % of the children and 44 % of the adults), and recovered to normal in 15 % of the children and 9 % of the adults.
- 4) if the muscle functioned well and was but slightly weakened recovery to normal occurred in 88 % of the children and 62 % of the adults.
- 5) the slighter the paresis was in children, the faster it improved (no material for comparison among adults) (Table 6).

Summing up, we may say of paresis of the extremities that:

- Total paralysis and severe pareses improve very little or not at all.
- The improvement is greater when more muscular function remained after the acute stage.
- The prognosis is generally better for paresis in children than in adults, except only for the severe cases; the less severe the paresis is in children, the more rapid is recovery.
- —Muscles only slightly affected with paresis may, in adults, recover completely, but complete recovery is very rare in cases of moderate paresis in adults, though more frequent in children. In the case of children even muscles severely affected may sometimes be restored to normal.

Even though the prognosis for individual paretic muscles is comparatively unfavourable, and though nearly 60 % of all patients were entirely paralyzed or suffered from severe paresis at the end of the acute stage, yet nearly all, even the high degree invalids, had noticeably improved during the follow-up period.

This last is due to the following reasons:

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1) The patients have learned to compensate for the paralyzed

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Table VII
Capacity for work at control examination

	Able			Invalidity a	Invalidity at control examination	examinatio	a		No.	%
Capacity for work	support	% 0 1	_II < 10 %	10-30 %	11 + 11 - 111 - 111 + 110 - 10 % $10 - 30 %$ $10 - 30 %$ $10 - 30 %$ $10 - 30 %$ $10 - 30 %$	111+ 5070%	VI 70—90%	V 90—100%	of	of total
1. Capable of heavy labour	+	15	19	1	i	1	1	1	34	38
2. Capable of light work only	+	1	60	9					10	11
3. Fit only for special trade	+			10	13	10	4		37	41
4. Fit only for special trade	6.					the book and you may have a	4		4	4.5
5. Fit only for special trade		. [7	84	4	4.5
6. Entirelyincapable of work	0 mm					1	1	-	1	-
		15	22	16	14	10	10	3	06	100

muscles with others, less paretic to begin with and since partly or entirely recovered.

- 2) The patient has learned to make use of his limbs in a new manner.
 - 3) Orthopedic treatment has been given.

Capacity for work.

Owing to the above facts, as also to the patients' adjustment to their changed condition and to new work, the average capacity for work of these patients as ascertained in the follow-up examinations was relatively high (Table 7).

38 % of them were fit for even heavy physical labour. A further 11 % were incapable of more than light work, and 41 % were fit only for some suitable special trade.

All of the above, adding up to 90 %, were able to support themselves by the proceeds of their labour. Included here are also the children considered able to support themselves in the future. Only one patient remained completely incapacitated for work; the remaining 9 % were either unable to support themselves entirely, or as yet their capacity for work cannot be determined with certainty.

»Shortening» of limb.

Shortening of limb was found only in patients under 15 years of age (Table 8), and this defect must be admitted to be the most serious consequence of the disease in this age group. The child in such cases is forced to rely chiefly on the use of their healthy limbs, which leaves the muscles of the paretic limb without much exercise, a condition easily leading to deformities of the limbs and trunk. It is also evidently due to the occurrence of limb shortenings, and the secondary afflictions arising therefrom, that the children suffering from severe paresis and some of those suffering from moderate paresis recover only comparatively imperfectly.

This shortening and its degree I found related to the degree and spread of paresis as follows:

Table VIII. shortenings of limb, in children A) According to invalidism at the end of acute stage

	Invalidism at the end	pu				*Shor	*Shortening* of limb	limb			
	of acute stage		Conside-	Partic-	Covere	Moderate	Slight	Short-	No	Short-	Total
	Class	%	measured	severe	SCACIO	Moderate	Sugar	(Totals)	ening	uncertain	Iorai
±	+ Cranial nerve paresis)	0	1	1	1	-	1	1	00	1	80
	-11	< 10		1			1	1	9		7
	+11	1030	1	1		1	9	8	4		7
	Ш	30-50	1		1	8	61	2	1	2	00
	+111	50-70	-	a	-	9		6	***************************************		6
	IV	70-90	41	1				5	1	28	7
			4	ത	61	80	9	23	19	4	46
		B	According	to worst	degree of	B) According to worst degree of paresis at the end af acute stage	the end s	of acute sta	age		
-	1. Total paresis		41	ဇာ	81	4	28	15	1	1	15
લં	. Particularly severe paresis	paresis	1	ı	I	1	1	1		I	1
က်	Severe paresis		1		1	2	i	61	1	318	9
4	. Moderate paresis		1	ı	-	1	4	10	+	1	10
7.0	. Slight paresis		1	ı	I	1			9	P	9
9	no paresis of limb		1		-		1		80	-	00
			4	03	22	00	9	23	19	4	46

¹ Severe atrophy of noth lower limbs in all cases.
¹ 14 years old girl, noth of whose legs were equally affected.
^a Paresis limited to a small area (<30 % invalidity).</p>

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s innited to a small area (<30 % invalidity).

- 1) In all patients more than 50 % incapacitated 1—2 mos. from onset of the disease, and who were than entirely or particularly severely paralyzed in some part of a limb, the paretic limb has remained shortened.
- The greater the general invalidism and the more severe the paresis in some group of muscles, the oftener this limb remained shortened and the greater the degree of shortening.

3) In cases of but slight general invalidism shortening occurred rarely, and even then only when the muscular paresis was at least moderately severe.

4) When only slight pareses occurred they were not followed by shortening. Moreover, I observed in a number of cases a shortening in only that portion of a limb in which pareses occurred.

Deformities.

Deformities of limbs or trunk were observed in 49 of the patients examined. The greater the degree of invalidism at the end of the acute stage, the more often deformities resulted (see Table 9 for details).

Aftertreatment.

Deficient home care had evidently adversely affected the condition of 18 patients or delayed their recovery. The greater part of these were children, and the most usual consequences of neglect of treatment were contractures of the joints and atrophies of the paretic muscles.

The blame for some of the mistakes in treatment must be attributed to the lack of proper surroundings and possibilities for care due to the war, but even in peacetime (and even in Helsinki) the aftertreatment of poliomyelitis patients as practiced in Finland doubtless leaves room for improvement.

In the whole of Finland there are at present reckoned to be over one thousand poliomyelitis invalids over 18 years of age and each year there are some 50 new invalid cases.

Deformities at the control examination Table IX

Invalidism at the end of acute stage	e end	Total number of cases	-	nation	Information No. of cases incomplete of deformity	ses	Trunk		Contracture of joint	cture	Flaccid	laccid joint	subluxation of joint	cation
Class	%	<15y >18	5 y < 15	> 15	<15y>15y <15>16 $<15>16$ $<15>16$ $<15>16$ $<15>16$ $<15>16$ $<15>16$ $<15>16$	15	< 15 >	> 15	< 15	> 15	< 15	> 15	< 15	> 15
I (+ Cranial nerve paresis)	0	L	1	1	1		1		1	i	1	i	1	ı
П	0- 30	15 16	1	1	8		1	5	8	1	1	i	1	
III	30— 70	17 10	j	1	13 9		9	9	6	-	4	4	i	1
Ŋ	70- 90	7 13	-	1	6 11		63	7	9	4	4	4	-	1
Λ	90-100	- 5	1	3	- 2		ı	1	1	2	1	1	1	1
Total		46 44	_}	4)	22 27		8 19	6.	81	-1	∞ }	∞)	-5	iz
		06		5	49	-	27		25		1	16		1

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It is to be hoped that the new invalid relief law now in preparation will improve the care of infantile paralysis victims, to whom it also applies, whether they be children or adult invalids. It cannot, however, reach its full effect until sufficient hospital beds can be provided.

Discussion on Papers 14-17 & 20.

Wallgren: Referred to an investigation carried out by himself and Dr. Lundholm with a view to determining the length of the interval between primary tuberculosis and bone tuberculosis. This investigation revealed that in half of the cases examined bone-tbc appeared within a year of the initial the-infection and in two thirds within two years, whereas very few instances were found of bone-tbc appearing three years after the infection had been communicated. Dr. RISINGER's eight cases also occurred within three years of the primary manifestations of tuberculosis. - I also wish to stress some of the conclusions of Dr. NATHORST's investigation. He postulated that the prognosis with regard to lung tuberculosis was less favourable in cases where the pleurisy appeared after the patient had attained 9 years of age than when the patient was under that age. In view of the fact that pleurisy generally develops within six months of positive reaction to tuberculin, infection contracted in later childhood would seem to be more dangerous in this respect as regards the possible development of pulmonary tbc. Further, I should like to bring special attention to bear on Dr. NATHORST'S conclusion that the reaction to tuberculin was not extinct in any of the children examined, which seems remarkable in consideration of certain reports from various countries which indicate that extinction of sensitiveness to tuberculin is fairly commonly recorded.

In Sweden there has been no increase in cases of lues congenita during the last ten years (1933—1943). The cases reported number 20 a year. With us, lex veneris has been in force for twenty years, and as our country has not been engaged in warfare, there has been no increase attributable

to war-time conditions.

ENEVIST: At the United States Public Health Service Meeting of Penicillin Investigators of the National Research Council, held at National Academy of Sciences, Washington D.C., on February 7th, 1946, the following summary of facts relating to penicillin therapy for congenital syphilis in the U.S.A. was given by Platou (Tulane University School of Medicine):

The number of patients treated for early manifest lues congenita was 191. The youngest was aged 11 days, the oldest 23 months. The mean age when treatment was started was $5\frac{1}{2}$ months. The cases had been

collected from four different clinics; only 23 of the children were white, the rest were coloured. The patients were treated exclusively with Sodium penicillin, the majority receiving 20,000—40,000 units per kg/body weight, given in 60 3-hourly injections for 7½ days. Larger schedules of 80,000 units per kg were given in 120 equal doses for 15 days. Serious reactions calling for interruption of the treatment were not observed.

Relapses were recorded in 12 cases, of which 5 were clinical as well as serological and 7 only were serological. 24 patients died while treatment was in progress, the deaths being attributed to common childish disorders such as broncho-pneumonia, nutritional disturbances, otitis media, congenital heart diseases, etc. Striking improvement was noticed in 64 patients showing abnormality in the cerebrospinal fluid, and the healing of visible lesions was dramatically rapid, while extensive osseous involvement healed slowly, usually in 3—5 months.

PLATOU'S concluding remark was that Sodium penicillin seemed to be the best agent yet employed in the treatment of congenital syphilis.

Thus, American penicillin therapy for lues congenita aims at effecting complete cure by means of intensive treatment during 1—2 weeks. It is natural that such an idea should have been conceived, and experiments carried out on patients with this end in view are quite justified. However, the dream of effecting 'sterilisatio magna' is by no means new in the history of syphilis therapy, and considering the very varying tendency for healing in lues congenita, a practitioner may perhaps be allowed to hold a somewhat sceptical view of this *all-or-nothing* attitude. On the other hand, this consideration indicates an investigation of the value of combining the penicillin principle with other methods of treatment. In view of conditions now prevailing in Finland — high mortality figures, vulnerability of all children on account of the low standard of nutrition, and unusually virulent infections — the use of penicillin would in my opinion be justified in the following cases:

- 1) as a remedy for severe intervening infections,
- 2) as shock-therapy, used in conjunction with some other treatment to ensure rapid serum-negativity in cases where this does not seem attainable by other means,
- 3) for initial treatment of feeble children who cannot endure any other kind of therapy.

During 1946, seventeen patients were treated with penicillin at *Haga Extra Sjukhem* while undergoing prolonged treatment af some other kind.

- 1. The patients reacted favourably to penicillin and generally put on weight during penicillin treatment.
- 2. After penicillin treatment the patients seemed to tolerate other forms of treatment better than before.

3. Acute infections of a fatal nature could be removed with penicillin and the luetic infection was simultaneously mitigated.

4. A remarkably rapid serological improvment usually took place after the administration of penicillin.

5. Penicillin treatment, like all other cures previously used, is apt to produce acute bowel atony, eventually developing into fatal anorexia, vomiting and loss of weight in feeble children.

Apart from the cases where penicillin has been used as above, syphilis therapy at the *Finlands Welanderhem* at Haga has consisted in repeated courses of treatment with series of Salvarsan or Spirocide, alternating with Bismuth or ointment cures. The therapy has been continued regularly for one year after serumnegativity has been obtained.

Sundal: In Norway, the incidence of venereal diseases, including hues acquisita, has increased considerably during the war. As a link in the campaign against syphilis the Board of Public Health recently decreed that all doctors, whether on the staff of hospitals, dispensaries, advisory centres or doing general practice, should perform a Wassermann test on every pregnant woman, the blood specimens to be examined free of charge at the State Institute for Public Health. We believe that this measure provides a safeguard against lues congenita, since it ensures latent acquired lues being diagnosed in time to allow the patient to be treated during pregnancy.

PLUM: At the children's department of the *Rigshospitalet* experience has taught us to defer hormone treatment until the patient has almost reached the age of puberty. Follow-up examinations of patients who have been operated on for cryptorchidism have unfortunately shown that the danger of sterility resulting is considerable. We therefore recommend operative treatment only in cases where complications occur in connection with defective descent at the age of puberty.

Sundal: The moderate hormone doses administered by me have not been observed to entail ill-effects of any kind. On the con trary, mothers of my patients have often reported spontaneously to me that their sons lose their shyness and nervousness and develop »boyish traits. In no case has lasting, fundamental destruction of the genital functions occurred. I do recommend interruption of treatment, however, in cases where no results are observed after administration of about 2500—3000 M.E.

MALMBERG: Dr. ELGENMARK was to have read a paper tomorrow on epiphyseal ossification in certain pathological conditions. On account of illness in his family he has been prevented from coming here.

His data comprise certain cases of cryptorchidism in infancy, coupled with distinct retardation in the epiphyseal ossification, which indicates

that endocrine disturbances manifest themselves also through other symptoms than cryptorchidism as such, appearing in conjunction with the latter.

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MALI: One of the patients cited in Dr. ARVELA's case-histories concerning serious forms of poliomyelitis in early childhood, is now being treated for second attack of poliomyelitis in my department of the Central Hospital of Pori. In 1937, of the aged of 4 years and 11 months, the girl was admitted to the Hospital for Infectious Diseases in Helsinki to undergo treatment for polyomyelitis. Her upper and lower limbs as well as the lumbar region of the back and the muscles of the stomach were paralysed on admission. At the end of one year she was completely cured and Dr. Arvela's followup examination in 1946 revealed no muscle atrophy. At the end of May 1946, when aged 13 years 7 months, she came to my consulting-room, having noticed that her lower limbs had grown weak and the gripping faculty of her hands impaired after a spell of fever lasting for two days one week previously. She was admitted to the hospital, where the following symptoms were observed on the day of admission: distinct bilateral paresis of the muscles of the hands and peroneus, multiple patellar reflexes; lumbar puncture: fluid clear, 81 cells per cubic mm (mono and polynuclear in equal numbers), Pandy +, Nonne -, sugar 90 mgm per 100, lumbar pressure 150 mm. During the following four days the paralyses increased, the knee-jerks became extinct, and finally the upper as well as the lower limbs and the muscles of back and stomach, became paralysed. Also considerable pain in the lower limbs was noticable. The general condition was good, however. 100 Gm heparine was administered four times a day for six days. Three weeks after admission, viz. about four weeks after the onset of the illness, there were slight of improvement of the paralysis. Now she can move her fingers fairly well and slightly raise her shoulders, thighs and soles.

When studying recently the case history of this patient for the year 1937, as recorded at the Hospital for Infectious Diseases in Helsinki, I was struck by its remarkable resemblance to the fresh onslaught of polyomyelitis ten years later with regard to the anamnesis as well as the course of the illness. On both attacks the initial fever stage lasted two days only, whereupon the illness progressed fairly slowly, the paralysis affecting the same sets of muscles and beginning to retreat in fairly quick stages after a lapse of three weeks. Even though heparine, which formed part of the treatment on the second attack, was not obtainable in the first instance, the cure has been satisfactory in both attacks of poliomyelitis, at least so far.

Ström: Since mention has been made of heparine in connection with treatment for polyomyelitis, I should like to call attention to the fact that by my orders every other case at the Hospital for Infectious

Diseases in Stockholm has been treated with heparine, since 1945, every alternate case serving as control. That is the only way in which the value of heparine in polymyelitis therapy can be ascertained on a scientific basis My experiences have been entirely negative so far, but the case material is still not extensive enough for me to give a final opinion. In the heparine series three deaths have occurred, as against one in the control series, and no difference has been observed as regards the progress or retreat of pareses, at least not to show any balance in favour of heparine.

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New classification and nomenclature for newborn infants including prematures and abortions.

By

ARVO YLPPÖ.

Everyone engaged in clinical or pathological work relating to the care of prematurely born infants knows how impossible it has been so far to compare the material of different pediatric and above all obstetric clinics. In some quarters the infants are still being classified according to their length at birth, no definite length having been agreed upon, however, 45, 47, even 48 cm being regarded as boundary lines for premature births. In another connection I have tried to prove that there is no advantage in going by length rather than by weight. Further, I have been able to demonstrate that the same nurse or midwife may attain different results, varying up to 10 %, in measuring the length of a child on successive occasions.

Yet, my proposal that 2500 g should be adopted as a distinguishing limit between prematures and full-term infants has also been advocated and even applied by many authorities. This distinction was officially adopted in 1935 by the American Academy of Pediatrics, and the Royal College of Physicians of London and the Royal College of Obstetricians and Gynecologists of England have also expressed agreement with my view.

But where should the lower boundary line for prematures be drawn? How shall prematures be distinguished from abortions? To us pediatricians the question seems a simple one. We draw the line as low down as possible, as children weighing 500—600 g at birth have been known to live for shorter or longer periods.

Obstetricians, however, regard the matter differently. In their textbooks, as in those on midwifery, it is stated, as a rule, (STÖCKEL and others) that if the pregnancy is interrupted before the 28th week the fetus cannot survive and that such cases should be regarded as abortions. As it is commonly admitted that it is often impossible to determine with certainty the duration of the pregnancy, one has tried to base the distinction on the length of the child, and 32 cm (sometimes even 35 cm) has been suggested as a distinguishing value between prematures and abortions. In Sweden for instance, all stillborn feti measuring up to 35 cm are regarded as abortions, while all feti weighing less than 2500 g, but having breathed and shown signs of life, are regarded as prematures, as also all still-born feti measuring from 35 to 47 cm.

In our country, v. Numers, trying to determine the mean weight of feti aged 28 weeks, which age is »popularly» and in the textbooks regarded as being the upper limit of abortions, has fixed the mean weight of feti aged 29 weeks at 1250 g.

This coincides with the weight advocated by Henderson (Journal of Obstetrics and Gynecology of the British Empire) last year as being the most suitable lower limit for prematures. For smaller feti he suggests the denomination *praeviable*.

v. Numers results, derived from Parviainen's considerable Finnish data, show that the mortality of children weighing between 600 and 900 g at birth is 100 % in the first year, and of children weighing 900—1400 g 97.2 %.

As the number of survivals among the children weighing less than 1250 g at birth was so small in his material, v. Numers arrived at the conclusion that the limit between prematures and abortions should be fixed at 1250 g, which would also tally with the prevalent popular, and textbook notion, according to which a fetus less than 28 weeks old is an abortion.

^{11 -} Acta pædiatrica. Vol. XXXV.

From the obstetric point of view this upper limit for abortions (28—29 weeks and 1250 g) would also be acceptable in so far as according to RITALA and others a woman should be regarded as secundipara only if the previous pregnancy has extended over 28—29 weeks.

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These questions were thoroughly discussed recently at a joint meeting of Finnish obstetricians and pediatricians.

Recent developments have made it possible to save a greater number of prematurely born infants and it may be said with certainty that the number of such cases will increase still further. Consequently, a greater proportion of the children weighing less than 1250 g at birth and classified as abortions will remain alive, which is bound to create a strange and untenable situation from a statistical as well as a practical point of view and necessitate a downward adjustment of the upper limit for abortions. On the other hand, the above mentioned obstetric considerations and the sudden drop in mortality figures at the weight of 1250 g or the age of 28-29 weeks, constitute an inducement to lay special stress on this weight and stage of development. Henderson speaks of »praeviable» children, Rauramo suggested »immature» children at the meeting mentioned above. The latter denomination has often been used as a synonyme for prematures, for instance by Peiper, who substitutes »unreife Kinder» for »frühgeborene Kinder», but this need not prevent our adopting the denomination simmatures, for a certain group of prematurely born infants.

In Finnish official statistics 800 g has hitherto been regarded as the lowest limit for prematures, but this figure might be reduced to 600 g in consideration of recent experiences and in view of the anatomical structure of fetus. Finnish pediatricians and obstetricians are agreed on this point, and on their behalf I would now like to propose that a classification based on the weight at birth should be officially adopted in the countries of northern Europe in respect of children and parturitions, when the weight of the infant does not exceed 2500 g, according to the following principles:

1st Group — partus praematurus, comprising children and parturitions for which a birth weight of 1250—2500 g is recorded,

2nd Group — partus immaturus — children and parturitions registering a birth weight of 600—1250 g,

3rd Group — abortus — all cases where the birth weight does not exceed $600\ g$.

Discussion on Paper 21.

LICHTENSTEIN: Expressed agreement with the principle of a group of immatures being introduced between prematures and abortions. The upper limit should be fixed at 1250 g for reasons advanced by Prof. Ylppö, whereas some hesitation might be felt in drawing the lower boundary line. Advocated the adoption of a uniform nomenclature in different countries.

YLPPÖ: The fixation of a lower limit is important mainly for two reasons:

1) different statistics would become comparable,

 the effects of maternity welfare could be more easily ascertained and compared than hitherto.

On the chemical proporties and clinical use of protein hydrolysates.

By

GUNNAR ÅGREN.

Since Mc Coy, Meyer and Rose's discovery 1935 of threonine and its indispensability to the animal system, numerous studies in animals and in man have been reported on the administration of amino acids derived from various sources. Using a complete mixture of amino acids in a synthetic diet, Rose et al. 1939, 1943 have shown that it is possible to keep dogs and human beings in nitrogen equilibrium. Also Madden et al. 1943 have obtained positive nitrogen balance with hypoproteinemic dogs injected with mixtures of the ten essential amino acids. In table 1 the essential and non-essential amino acids are recorded.

Table 1.

Essential amino acids	Non essential amino acids
Arginine	Alanine
Histidine	Aspartic acid
Lysine	Citrulline
	Cystine
Isoleucine	Glutamic acid
Leucine	Glycine
Valine	Hydroxyproline
Threonine	Hydroxyglutamic acid
Methionine	Norleucine
Phenylalanine	Proline
Tryptophane	Serine
	Tyrosine

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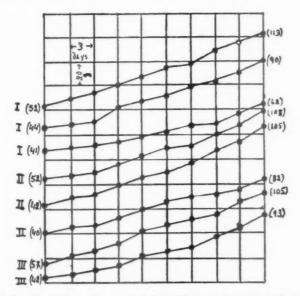


Fig. 1. Growth of rats on the standard diet with an addition of protein hydrolysate. When calculating with an average body weight of 50 g the animals of group I and II were given a volume of hydrolysate corresponding to 1.5 and 3.0 g respectively of protein per kg of body weight and day. Group III = control animals. The numbers in parenthesis denote initial and final weights of the rats.

From pediatric point of view it is of special interest that in the food of growing animals these ten essential amino acids must be present. In consequence they have also been called »vitamino-acids». Recently several investigators have studied the oral and parenteral administration of protein hydrolysates containing the essential amino acids (cf. Wretlind 1945). The hydrolysates have been prepared in two ways, either by acid hydrolysis of proteins, mainly casein, fortified with tryptophane, (Parenamine, U.S.A.), or by enzymatic hydrolysis, (Amigen, U.S.A., Aminosol, Sweden), the source of enzyme being the digestive organs.

Two years ago, in connection with investigations on factors stimulating the formation of blood corpuscles, I was interested in the action of the catheptic enzymes on proteins containing extrinsic

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Table 2.

Amino acids in per cent of ash and moisture free protein with a calculated nitrogen per cent of 16.0 A = Enzyme hydrolysate. B = Enzyme hydrolysate further hydrolized 4 hours with 20 p.c.HCl. C as B but with 20 hours acid hydrolysis.

	A	В	С
Arginine	4.8	4.9	3.9
Histidine	1.3	1.3	1.1
Lysine	10.5		6.7
Valine	2.9	3.9	6.9
Isoleucine	3.6	4.8	5.9
Threonine	4.9	6.3	6.6
Methionine	2.7	-	2.1
Phenylalanine	6.3	_	3.5
Tryptophane	1.3	0.30	0.33
Cystine	0.6	0.80	0.75
Tyrosine	6.4	5.5	4.9
Glycine	2.6	2.9	2.8
Proline	4.9	11.8	12.0
Hydroxyproline	0	C	0

factor (casein). It was found that an almost complete proteolysis could be obtained. The quotient amino nitrogen to total nitrogen was repeatedly determined to 0.60—0.65 (ÅGREN 1946 a). The reaction was performed at weakly acid reaction and the method therefore offered certain practical advantages in the large scale preparation of a protein hydrolysate. The effect of the hydrolysate was tested on growing rats. They were kept in individual cages and fed a diet used by GARD in order to obtain a maximal growth. The protein hydrolysate was administered orally with a pipette. The rate of growth of the animals in the experimental and in the control series was the same (cf. Fig. 1).

It was observed, however, that the food intake of the rats in the experimental series (hydrolysate + diet) was significantly less than that found in the control series, (ÅGREN 1946 b). This observation was related to the report of Wolley 1945 that enzymatic protein hydrolysates contained specific bacterial growth stimulating substances of peptide nature. The results reported in the present investigation on rats has recently been confirmed by Rose et al. 1946.

The results of the rat experiments prompted an investigation of amino acids and enzyme-resistant peptides in the protein hydrolysate. A chemical analysis was carried out on the hydrolysate directly and after a further acid hydrolysis. The preliminary results are given in Table 2.

Of the 20 amino acids found in casein 14 have been analyzed with a total yield of 66 p.c. If the figures found by WILLIAMSON for the remaining amino acids are added a total yield of 115 p.c. is obtained. The amounts of essential amino acids in the hydrolysate must be considered as satisfying from nutritional point of view as the result approaches that found by HIER and BERGHEIM 1946 for the pattern of free amino acids in human plasma. Comparing the figures obtained directly on the enzymatic hydrolysate and those found after a further acid hydrolysis it is obvious that of the 13 amino acids found 9 are set free while valine, isoleucine, threonine and proline seem to form peptide bonds rather resistant to the action of the catheptic enzymes. This result from pediatric point of view is of special interest in connection with the therapeutic use of protein hydrolysates on premature children. It seems possible that these enzyme-resistant peptides may have a similar extra growth effect on children as found on rats. If demonstrated, this effect would favour the exclusive use of enzymatically hydrolyzed proteins when a rapid growth effect is desirable. The isolation and chemical characterization of these growth factors must be of both theoretical and practical interest. The catheptic digested casein hydrolysates have been tested for more than a year on the Pediatric Clinic of the Academic Hospital, Uppsala. The preliminary results of this investigation will briefly be communicated by dr. ÖBERG.

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Discussion on Paper 22.

ÖBERG: Following ÅGREN'S account I should like to tell you of some preliminary results of experiments with the casein hydrolysate in question used as subsidiary nourishment for premature children. The investigation is now in progress at the Children's Clinic in Upsala and was started just over six months ago.

In order to obtain fairly reliable basic data for purposes of control the investigation has been planned in the following manner. The children are placed successively, on reaching the age of one week, in one of the following groups:

Group I. Basic diet 120 cal/kg. breast-milk.

Subsidiary diet: 12.5 cm³ kasein hydrolysate (20 % amino acids

and 20 % glucose) per kg, equalling about 20 cal. per day.

Group II. Basic diet as group I.

Subsidiary diet: 10 cm² 25 % mixture of glucose + 2.5 g

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Subsidiary diet: 10 cm³ 25 % mixture of glucose + 2.5 g kasein per kg/about 20 cal.

Group III. Basic diet as in groups I and II.
Subsidiary diet: 30 cm² breast-milk per kg/about 20 cal.

By this means the calorific value per kg is kept on the same level in all the different groups. The birth-weights have varied between 2240 and 1350 g. As debile children are very tricky material from a nutritional point of view, the data will have to be fairly extensive before definite results can be obtained from an investigation of this kind. The number of cases is still very small. I present the average figures for the weight increase during the 2nd and 3rd weeks after birth:

The difference in weight increase between groups I and III is so pronounced that it may be assumed that it will remain appreciable even. a larger number of case histories. It is yet too early to say anything further. The children have taken the preparation fairly well in spite of the unpleasant taste.

The Development of Rickets in Premature Infants.

By

GERT v. SYDOW.

About 30 years ago, Ylppö in his studies of premature infants had come to the conclusion that the low content of bone-building minerals in human milk must sooner or later cause rachitic changes in premature infants given this food exclusively. This opinion has since been supported by several observations especially those made by American investigators. Thus, analyses of fetuses at different stages of their development have shown that the mineralization of the skeleton is to a very large extent brought about during the last intra-uterine months, so that premature infants, it must be assumed, are born with a considerably less mineralized skeleton than full term infants. Further in metabolism trials on infants it has been found that the mineral retention which can be attained by feeding exclusively on human milk is not sufficient to maintain the mineral content per kg body weight of the infant at birth. It is not surprising, then, says an American author, that premature infants who have been fed only on human milk almost invariably develop rickets.

Since, however, the mineral content decreases considerably after birth even in fullterm breast-fed infants, but is maintained at the original level if the infant is given cow's milk, many authors have interpreted this decrease as a physiological one, whereas the continually high mineral content in bottle-fed infants has been

termed *supermineralization* and has been regarded as, if not harmful, in any case probably not useful. This opinion, of course, seemed to be supported by the practical experience that clinical rickets is found, proportionally, more often in bottle-fed infants than in breast-fed ones. This, probably, is the reason why the recorded observations on premature infants have not received much attention, and why almost all modern text-books of pediatrics teach that rickets caused by a lack of minerals can only be provoked in certain species of animals, but not in infants. Rickets in infants is usually described as an almost pure avitaminosis, and this the more categorically, the newer the text book.

To me, it was therefore a surprise when, some years ago, I was trying to investigate the possible difference in vitamin D demands between breast-fed and bottle-fed infants, and found that when, of a pair of premature twins, one twin was given only human milk and the other a supplement of cow's milk, the blood of the human-milk twin would consistently show lower values for serum inorganic phosphorus and higher for serum phosphatase than that of the cow's milk twin, and in some cases the human-milk twin also developed roentgenological signs of rickets, while the cow's milk twin showed all the time normal roentgen pictures.

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I then began to investigate the part played by feeding in the development of rickets in premature infants and have now collected the results from a series of such infants with birth weights not above 2000 g. The infants have been examined regularly, usually at intervals of 14 days, with roentgen and blood analyses: microanalyses of serum phosphatase, serum inorganic phosphorus, and serum calcium. As a check and for comparison I have also examined by the same methods a series of normal full-term breast-fed infants, on the one hand newborn, examined at the obstetric ward, on the other hand older infants examined at a children's welfare centre. The normal values obtained agree very well with those reported in recent years by other investigators, mostly from America.

If the premature values are compared with the normal, it is found that in the first days of life the serum phosphorus is the

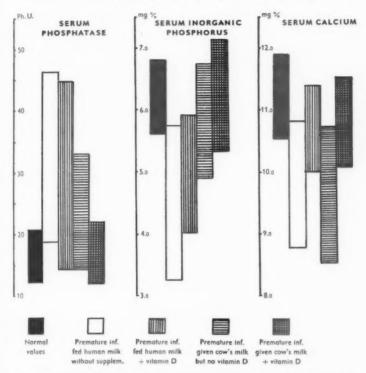


Fig. 1. Premature infants, birth weight 1010—2000 g; serum values at 16—105 days of age after different feedings.

same in the premature as in the fullterm newborn. The serum phosphatase is about $1\frac{1}{2}$ times as high in the prematures as it is in the full term infants and the serum calcium is about 1 mg% lower in the prematures. In the following months the values depend greatly on the feeding of the infants, and this is shown graphically by the diagram (Fig. 1) for the age period 16—105 days. The columns represent the means of the groups \pm the standard deviations, i.e. the range within which about two-thirds of the individual values may be found.

The serum phosphatase is low in the full-term normal infant

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and has a very small standard deviation. In premature infants given human milk without any supplement it is on the other hand, very high: the mean is about twice, and the standard deviation about three times the normal. - A supply of vitamin D in a large dose does not seem to make any difference in this respect, A supply of cow's milk, on the other hand, makes the values considerably lower, though still higher than the normal. - A supply both of cow's milk and of vitamin D, finally, makes the values quite normal, and even the standard deviation becomes as small as in the normal series. — It will thus be found that a supply of cow's milk will bring the serum phosphatase nearer the normal in premature infants, and that the effect of cow's milk in this respect is improved by vitamin D supply. A supply of only vitamin D, on the other hand, seems not to have any effect. This is true, in any case, for the smallest premature infants; in the somewhat larger ones a small effect can really be shown of a vitamin D supply only.

The serum inorganic phosphorus is high in the normal series, with a fairly small standard deviation. Premature infants given human milk without any supplement, show a considerably lower mean and a standard deviation which is about twice that of the normal series. — A supply of vitamin D causes no statistically significant improvement. A supply of cow's milk, on the other hand, causes a considerable improvement, and if both cow's milk and vitamin D are given, the values become about normal, but the standard deviation is still somewhat larger than the normal. Thus on the serum phosphorus, too, the cow's milk supply, has the main effect. The simultaneous addition of vitamin D will, possibly, give still better values, but its effect is not statistically significant.

Finally, the serum calcium gives quite a different picture. Like the phosphorus, the normal mean is high with a fairly small standard deviation, and like the phosphorus, the premature infants given only human milk show low values with a large standard deviation.

— But in this case, cow's milk supply has no effect. Premature infants given a cow's milk supply, but no vitamin D, have as low a mean and as large a standard deviation as the infants given human milk without vitamin D. Here, on the other hand, some effect will be obtained by vitamin D. Premature infants given

human milk + vitamin D show a considerably better mean and a very small standard deviation. The supply of cow's milk + vitamin D gives the same result. Thus cow's milk cannot improve the effect of vitamin D on the serum calcium.

The main effect of vitamin D, therefore, on the serum values is, that it improves the serum calcium. Cow's milk, on the other hand, may increase the serum phosphorus and decrease the serum phosphatase considerably. At least for the phosphatase, the effect of cow's milk may be improved by a parallel supply of vitamin D.

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The same effect as of cow's milk seems to be obtainable to some degree by giving certain mineral preparations, such as calcium hexosediphosphate. This may indicate that the effect of the cow's milk is due to its mineral content.

Regarding the roentgen findings it appears that skeletal changes which are usually interpreted as rachitic, can occasionally be found as early as on the 14th day, but from the age of one month they are found in more than half of all examinations. Neither a supply of vitamin D nor one of cow's milk can with certainty prevent the development of roentgen signs of rickets, but they develop only occasionally under cow's milk treatment. In a few cases, however, obvious roentgen signs of rickets have developed in infants given both a cow's milk supply and a large dose of vitamin D since the first week of life.

When the roentgen findings are compared with the blood analyses, the results are illustrated by fig. 2, for the age group 31—105 days. In this, no division is made between the serum phosphatase and phosphorus values of premature infants given no vitamin D and of those given vitamin D, as the vitamin does not have any noteworthy influence upon these values. For the serum calcium values, no division is made between premature infants given or not given a cow's milk supply, as the cow's milk has no effect upon the serum calcium values.

As will be seen from the diagram, the serum phosphalase of the infants given human milk is much higher in the cases which show signs of rickets than in the cases showing normal roentgen pictures, and the standard deviation is also much larger when

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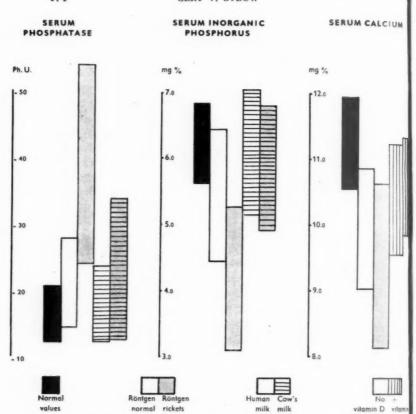


Fig. 2. Premature infants, birth weight 1010—2000 g; serum values at 31—105 days of age when roentgen findings are normal and when signs of rickets are present, with different feedings.

(Note that in serum phosphatase and serum inorganic phosphorus the blank colums represent human milk feeding with or without vitamin D, but in serum calcium means there has been no vitamin D supply, with human or cow's milk.)

rickets is present. In the cow's milk series, on the other hand, the difference is much less: even the infants with roentgen signs of rickets now show fairly normal values.

The serum inorganic phosphorus values, too, are much more normal in the cases given human milk where no roentgen changes have appeared. In the cow's milk series, on the other hand, there is no difference between those showing and not showing roentgen signs of rickets. In both cases the values are high and nearly normal.

The serum calcium values, on the other hand, in the infants given no vitamin D are lower when no roentgen signs of rickets have appeared than when rickets is present, but the difference is not quite significant. In the infants given vitamin D, on the other hand, there is no difference between the cases with and without roentgen signs of rickets.

Thus, cow's milk improves the serum phosphatase and serum inorganic phosphorus, even where it cannot prevent roentgen signs of rickets; and vitamin D improves the serum calcium even in the cases where rickets has developed.

Is it then really rickets, which thus manifests itself in the roentgen pictures and the serum values of the premature infants given human milk? No doubt, it may be objected that it is not proved that the anatomical basis of these changes is the same as is usually defined as rickets. I have planned, in collaboration with a pathologist to examine the anatomical material which during the investigation I have collected from premature infants who died in the hospital. Till now, however, this has been possible only with a few selected cases who have been examined by Dr. Stig RANSTRÖM, of the Pathological Institute at Upsala. The cases selected include those infants of the series who were oldest at their death, and they include both cases which had shown rachitic changes in the roentgen pictures and in the blood analyses; cases which had shown only pathological blood analyses but no roentgen rickets, and also cases which had shown neither roentgen nor serum signs of rickets. The results of the anatomical examination appear from the table (Fig. 3). Dr. RANSTRÖM has examined the costal epiphyses both macroscopically and histologically; histologically, he has tried to classify the degree of the changes from moderate (I), to pronounced (II), and severe (III). He says that the histological changes, where such have been found, have been quite typical for rickets. He points out the partial disagreement between the macroscopical appearance and the histological changes: pro-

Birth weight		Most recent analyses				Age at	Macro-	Histol.
		Age	Ph-ase	P	Rtg	death	scop. bosses	rickets
1530	human	9	9.6	2.35	_	19		0
1100	human	17	25.3	2.20	()	20	(+)	1
1560	human	19	19.8	4.20	-	24	-	11
1620	human	9	10.5	3.40	_	28	_	11-11
1550	hum.+gluc.	30	29.8	3.65	+	35	+	1
1940	human	29	36.8	4.95	()	44	-	0
1770	hum.+gluc. +cow's m.	48	16.0	5.45	-	57	-	0
1540	hum.+vit. D	50	16.8	4.55	_	65	+	0-1
1420	hum.+gluc. +cow's m.	88	44.4	4.00	++heal.	90	+	Ш

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Fig. 3. Comparison between clinical and anatomical findings in 9 premature infants who died.

nounced histological changes can be found without bosses, and bosses without histological changes. (This may be a memento concerning the value of so-called clinical signs of rickets: when no certain conclusions can be drawn from the bosses at a free-prepared and split rib, what can be said of a rosary palpable through the skin?)

It appears from the table that the cases showing roentgen signs of rickets did also histologically show rickets of different degrees. That no roentgen signs of rickets were observed in some cases which had histologically pronounced or severe rickets, may be fully explained, at least in one of the cases, by the fact that the roentgen picture was taken so long before death, and at so early an age that signs of rickets were hardly to be expected. No histological rickets was found in a case showing a remarkably low serum phosphorus value but in other respects normal findings and in one showing a high serum phosphatase as the only sign of rickets. — The essential result of the anatomical examinations, however, is that the signs of rickets found at the investigation may correspond to a histological rickets, and that histological changes quite typical of rickets may be found as early as at the age of twenty days. This seems to indicate that the signs of rickets found in this material really are signs of genuine rickets.

On the absorption of calcium and phosphorus.

By

O. MELLANDER.

An account is given of preliminary experiments on the absorption of calcium and phosphorus in infants. The Ca/P ratio of the stomach contents of infants fed with human and cow's milk were determined. After digestion for 30 minutes in the stomach the ratio Ca/P was reduced in most of the experiments involving human milk. This was also the case in a few experiments with cow's milk but generally the ratio in these experiments was not reduced after digestion. That a secretion of phosphorus in the stomach does not occur was also established. The reduction in the Ca/P ratio therefore seems to indicate that absorption of calcium from the stomach is possible under certain circumstances.

The preparation of calcium phosphopeptone from cow's casein was also reported. This substance may be of importance for absorption of calcium and phosphorus in the intestines. It is not digested by proteolytic enzymes in the intestines, its content of calcium and phosphorus is rather high (according to preliminary analyses ca 10 % Ca and 6 % P). The calcium phosphopeptone is very soluble in water. Calcium and phosphorus in this form probably do not interfere with each others absorption (due to the precipitation of inorganic calcium phosphate) which might be the case when they are given as inorganic salts.

25.

The Principle of Evacuation of the Stomach in Infants and Prematures.

A non-roentgenologic study.

By

S. VENDEL.

For several decades the motor function of the stomach has been the object of comprehensive investigations (cfr. Catel 1937), but despite the minute observations of many experienced investigators the separate results will be seen to differ so much from each other that it is still possible only to speak about the emptying of the stomach in the most general terms. The time of evacuation varies very considerably in different individuals, and even in the same individual on repeated examination. A fairly great variance is found between different groups, e. g. when comparing a number of works of the medical literature, as did Bousloug (1935).

Therefore, SMITH (1945), is fully justified when he writes as follows: »No uniformity is to be expected. The stomach empties with unpredictable variability», but it is difficult to imagine that this should really apply to infants who in most of their other vital functions display so marked a regularity. It has been tried to explain the variations found from the affectibility of the stomach by its reflex and hormonal regulation. On the other hand, in CATEL's statement (vol. I, page 121) the following description of the gastric peristalsis is found: . . . »eine Präzision der rhytmischen Tätigkeit, die übervascht . . . kaum um Bruchteile differierend»!

Nearly all investigations are roentgenologic. In most cases a contrast medium was employed, but a few investigators have

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wanted to safeguard against possible methodic errors caused by this examination and made the transillumination without using barvtes, as did Behrendt (1923) and Bessau, Rosenbaum and LEICHTENTRITT (1921). The predominant use of the roentgenologic method must be attributed to the fact that it has been believed that all factors changing the natural course of the evacuation could be avoided: The process can be followed without interference and the peristalsis observed, and it can be seen direct when the last residue leaves the stomach; and, if desired, these impressions can be fixed on a roentgen film. With some practice a certain perception of the course is obtained from the extent and density of the roentgen shadow: In some cases it will be seen that to begin with the stomach empties more rapidly, later on far more slowly while, in other cases, the reverse seems to be the case. The flaw of the roentgenologic method is that, besides making the peristalsis visible (and showing, when the first portion of the meal enters the duodenum, if a barium meal has been given) it gives only one exact item of information: The time when the stomach gets empty and that with so great variations that, in spite of everything, the method must be suspected of being encumbered with great sources of error. It gives no useful information about the entire intervening part of the evacuation curve, and cannot do so either until methodics have been prepared like that used in determination of the volume of the heart in vivo.

Both evacuation curves have their adherents among physiologists. The divergence of opinions is perhaps best illustrated by the following quotations: Starling: »As emptying proceeds, the rate of evacuation is readily slowed down by influences, probably reflex, but also in part hormonal...», and by Wigger (1934): "The emptying rate of the stomach increases progressively from the onset to the completion of digestion."

Only through quantitative determinations in the course of the evacuation will it be possible to elucidate which type of emptying is the right one. Such determinations are found only exceptionally in the literature, but Wilson's statements afford an example. Graphic representation of his table values conveys the impression that the nature of the food itself determines the type of evacuation:

Raw egg-white represents the former — the *concave* curve; whereas egg-yolk with bacon results in the *convex* shape. By fluroscopy an estimate was made of the percentage of the barium remaining in the stomach after $1\frac{1}{2}$, 3 and $4\frac{1}{2}$ hours.

As the times of evacuation in infants displayed so wide limits of variation, even a rough method with comparatively great experimental errors will be justified if only it elucidates one new feature of the evacuation of the stomach, be it either so that the variations have been due to the natural conditions or have simply reflected hitherto unnoticed methodic errors in the roentgen examination.

In the present investigation our aim has been to follow the entire course of evacuation, and not to be content with determining the initial and terminal points of the curve. The method we chose was simple use of an ordinary stomach tube (size 12 to 14) and a graduated Record syringe of 50 or 100 cm3. The rate of evacuation is followed by emptying the stomach at regular intervals (by means of suction with the syringe), measuring the quantity removed and then injecting it again into the stomach until it is time again to remove it with the stomach tube. Unfortunately a permanent tube cannot be used in infants, the tube has to be introduced again for each determination. It would moreover be desirable to be able to empty the stomach completely and refill it without changing its volume in the course of the procedure, to avoid stimulation of the peristalsis. This is possible only when using a Miller-Abbott's double channel tube, which is of too coarse a caliber for this examination in small infants. Besides it proved possible to arrive at useful results without these precautions and then to reduce the number of necessary introductions of the tube, so that disturbances originating from the use of the stomach tube were completely eliminated from the result of the experiment.

The basis of this communication is a series of 110 experiments, carried out on 27 children, aged 1 week—11 months. Of these 3 were examined shortly after gastrontestinal disturbances, and in 5 cases pharyngitis was present. In the rest of the children only disease of minor importance to gastric function, or no disease at all was present. A number of formulae were given: mother's milk,

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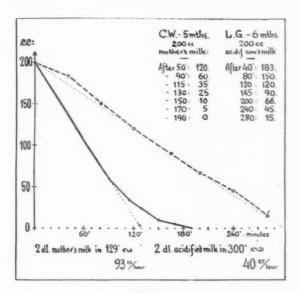


Fig. 1.

acidified milk, etc., to exemplify any commonly used formula, but the material hitherto collected being by this reason too small and too heterogeneous to give exact informations of the various emptying times, yet will allow certain preliminary conclusions about the process of evacuation:

1) In most infants the stomach empties completely regularly, despite the disturbing influence of the stomach tube; the evacuation proceeds with the precision of clockwork till at least 2/3, or sometimes 9/10 (or the whole) of the meal, has left the stomach, then its emptying rate decreases somewhat. With this qualification it can be said that the stomach empties a constant amount per time unit almost during the whole of the meal. In graphic representation it means a rectilinear curve. If this line, t, is elongated (extrapolated) till it intersects the zero line, the result will be a time which might be termed the ideal emptying time for the meal in question and which it would be possible to express in minutes.

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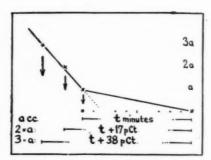


Fig. 2. Result of CRIDER and THOMAS' investigation grafically reproduced: a curve resembling the last part of our curves.

The number of minutes required by the stomach to empty 100 cm³ is an exponent of the emptying rate, but in comparisons between the emptying times of children at different ages then inverse proportion, i.e. the amount emptied per hour, is advantageously used as emptying coefficient $(=c_t)$. The quantity c_t varies inconsiderably as long as it is not determined for very large or very small meals: the linear curve applies within wide »normal limits». This conception of the emptying process is seen to be in full harmony with the results of CRIDER and THOMAS' investigations: »After larger meals the emptying time is greater in most subjects than after small meals; e.g. doubling a small test meal may increase the time by 17 per cent, and trebling it may increase it by 38 percent.» An approximate prolongation of 100 and 200 per cent should have been less confusing than these 17 and 38 per cent, but we have to reckon in most cases with a course of emptying, different from the »ideal». The reasoning is elucidated best by the curve (fig. 2). In this connection also Bouslougs statement wit would appear that feeding before the stomach was empty did tend to lengthen the emptying time» finds its natural explanation. The same holds good of the observation that debile infants would empty their stomachs more rapidly than normal infants — they get smaller meals!

2) c_t varies fairly moderately in the individual child from time to time, there is a somewhat greater variation between individuals

within the same age group. Our material does not yet allow the exact determination of the variance (σ) .

- 3) On comparison between the mean figure for c_t of the different age groups it is seen that this constant increases regularly month after month for each kind of food in proportion to the growth of the child. If c_t is, therefore, divided by the normal weight for the age in question, a quotient results which is nearly constant all through infancy for a definite sort of food or milk mixture, whereas in prematures it is found to be decreased in proportion to the debility of the child, expressing its functional insufficiency.
- 4) This reduced emptying coefficient is of typical magnitude for each kind of food. The ratio between these coefficients is found to be fairly unaltered on determination of the $c_{\rm t}$ of the single milk mixture in the individual child. Bearing in mind the experience of previous researchers about emptying times, it is astonishing to see how moderate the deviations in this ratio are as compared with the mean figure.

Exact, statistically tenable determinations of these figures are being prepared and will be published in a subsequent paper, in which reasons of individual variations will also be discussed; the paper will also comprise investigations into the conditions which, in our opinion, determine the different emptying coefficients for the various kinds of food in infants.

¹ These investigations were continued by Walter Keller during the second half of the year 1946 and along the same lines. The results arrived at by him further support the presumption, that the evacuation coefficient is fairly constant. He besides pointed out the existence of a striking proportionality between evacuation coefficient and body surface (calculated according to DuBois' formula), irrespective of the infant's age and said to hold good for prematures also. (Lecture held on the 14th February 1947 before the Pediatric Section in Stockholm.)

Presuming that the opinion expressed by von Pirquet is correct, viz.: that body surface and resorbing intestinal surface are directly proportional, this would imply that ct/surface unit of the intestine is constant, in other words: that every square centimetre resorbing surface of the intestine is supplied with an equal volume gastric contents per time unit irrespective of the infant's size and age — the resorption ability in children of different size and age is taxed in exactly similar degree by the same food.

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Comment:

What in this text was denoted as the evacuation curve of the stomach, actually represents a curve showing only the real evacuation less the quantity of gastric juice secreted during the same period and admixed to the stomach contents. This differential curve is rectlinear, although the gastric contents are subject to a confinuous dilution and acidification during the period of evacuation. This condition indicates that the acid and the concentration of food substances, within normal and fairly wide limits, do not exercise any great influence on the evacuation of the stomach. The most natural explanation for a rectlinear differential curve should be that it appeared as a difference between two straight curves rather than as a difference between two »convex» ones. Consequently it is presumable that the true evacuation curve turns out to be rectlinear (and that the course of the gastric secretion is entirely continuous in infants, as it has been deemed probable by several investigators) but this, however, still remains to be proved, and so far must serve as a hypothesis only.

Summary.

By roentgen only the initial and final points of the evacuation curve of the stomach can be determined exactly enough. To follow the entire course of evacuation another technic was applied: the volume of gastric contents being measured at regular intervals by aspiration through a stomach tube. It was demonstrated that the stomach in infants empties with extreme regularity, following mostly a rectilinear curve, the emptying rate depending upon age and the constituents of the meal, and the variations tending to be much more confined than previously accepted.

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A case of alimentary fatty liver.

By

FRITZ KARLSTRÖM.

The case is one of a girl, born on 1/4 1945. She was admitted for the first time to the Children's Department of the Karlstad Hospital at the age of 6 months and has since been nursed there twice.

Nothing of hereditary interest, First child. Partus normal, Birth weight 4,020 g. The child was entirely breast-fed up to the age of 2 months, when she was examined at an infant welfare centre and nothing was found to arouse comment. Soon afterwards the breast milk began to fail, and the patient then received additional food, and at the age of 3 months was being entirely bottle-fed. An old recipe from the child's paternal grandmother was followed, the mixture in the bottles consisting of 1/3 thick separated cream + 2/3 water + 2 tablespoonsful of milk sugar and one tablespoonful of wheat flour per litre of the mixture. The cream was extremely thick and almost of the consistency of syrup. (On two occasions I investigated the fat content of the cream, using Gerger's centrifuging method, and found it to be 52 % and 36 % respectively. The fat content in the diet which the child received for 3 months can thus be estimated as having been about 15 %!). The child received 5 meals per day, and as much as it would take at a time. At first she got on well, but in association with an infection at the age of 5 months, she began to vomit violently immediately after meals. Occasionally her motions were loose but for the most part firm and yellow in colour. The child had never been given cod-liver oil. She was admitted to the hospital for the vomiting and poor general condition.

On admission (at the age of 6 months) the general condition was moderately affected, turgor and tonus reduced, the patient was pale, so dehydrated that the skin could be lifted in large folds, the fontanelles sunken in. The face had a somewhat strange appearance, with fat, hanging cheeks exhibiting an abundance of veining. Weight 5,120 g. No fever.

Sed. rate 5 mm/1 hr. Cor, no findings. Pulm. no findings. Abdomen: fairly large. Liver enormously enlarged, its lower edge extending the breadth of a finger down over the navel plane and down to Crista iliaca. The surface was even and the consistency firm. The spleen could not be palpated. Blood: Hb. 106 %, Red blood corpuscles 4.6 mill. White blood corpuscles 16,200. Diff.: Staff nuclear 4.5 %, Segment nuclear 35.5 %, Eos. 1 %, Lymphoc. 47.5 %, Monoc. 11.5 %. Bone marrow (Nordensson): »Preparation abundant in cells. Myelopoiesis toxic. Megakaryocytes normal. Reticulum very strongly hyperplastic — in places large cells abundant in protoplasm of the type found in the case of different »speicherungs» diseases. Very strongly reactive marrow.» Prothrombin determination 25 sec. (normal time 21 sec.). Meulengracht 1: 5. Blood phosphorus 4.9 mg %, blood calcium 9.9 mg %. Hijman v.d. Bergh; neg. both direct and indirect reaction. Tokata: no flocculation. Cholesterin 233 mg %. W.R. neg. Urine: Heller: —. Almén: — Legal: — Gerhard: — Sed.: 0 pathological. Faeces: porridge-like, light yellow. Weber: - Katalase reaction +. Fatty acid needles: scanty. No iodophil substance.

On the suspicion that this might be a case of Glycogenosis, repeated fasting tests were made for blood sugar, and the 24-hour curve of the blood sugar and the glucose and adrenalin loading were observed. All these tests of the carbohydrates metabolism were normal, and therefore Glycogenosis could be excluded. To endeavour to ascertain the nature of the swelling of the liver, a liver puncture was made, which now, as in the later punctures, was very successful, and the patient did not appear to be injured in any way. The histological picture of the liver punctate, as well as the size of the liver on the occasion in question, is shown in the

figures below.

On account of the vomiting and diarrhea the patient was given 500 g of milk + tea at first, and subsequently citrido milk was added. The patient's appearance became more and more normal, the vomiting decreased and ceased almost entirely, and the motions gradually became normal. Her weight increased by nearly 1.5 kg in 7 weeks. The size of the liver decreased successively, and 47 days after her admission it was hardly larger than normal (its lower edge reached 1 finger's breadth below the edge of the ribs). A fresh liver puncture was now made (see fig. 2).

In order to ascertain whether a diet abundant in fat would again lead to enlargement of the liver, with the parents' consent, the same mixture with cream as the child had had in her home (720 g per 24 hours in 6 meals) was administered. The patient gradually began to exhibit the same appearance as when she was admitted, i.e. fat cheeks with veining, but not to the same degree as when she was admitted to the hospital. The child vomited moderately, and the motions became loose and yellowish-green. The patient was never affected. The size of the liver gradually increased again, and 28 days after the fatty diet had been begun, its lower edge

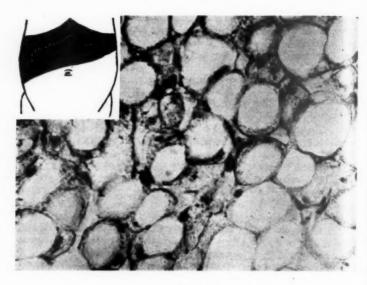


Fig. 1.

was 3 fingers breadth below the edge of the ribs and almost down to Crista iliaca. The spleen was again not palpable. Fresh liver puncture (see fig. 3).

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The patient was again placed on a normal diet (2/3-gruel 150 g \times 5 \div vegetables, fruit juice and vitamin D) and was discharged. She was readmitted to the hospital after a full month. Her weight had then increased to 7,770 g (about 1 kg in 1 month), and her appearance was that of a healthy child. The lower edge of the liver could be felt one finger's breadth below the edge of the ribs, that is to say the size of the liver was now normal. A 4th liver puncture was made 47 days after the child had been put on a normal diet (see fig. 4). The patient was sent home some days later and since then has got on splendidly.

Histological investigation of the liver punctates:

The following fixatives were employed: Abs. alcholol for fixation of the liver glycogen. 3 % BaCl₂ for 3—6 hours, with subsequent treatment with 10 % neutral fomaldehyde, to fix the preliminary stages of the gall, (according to Forsgren), and finally, a piece was fixed with 10 % neutral formaldehyde for frozen sectioning and fat staining. The glycogen was stained according to Best. The BaCl₂-treated preparations were stained with Mallory and the fat with scarlet-red (all the micro pictures are not published here).

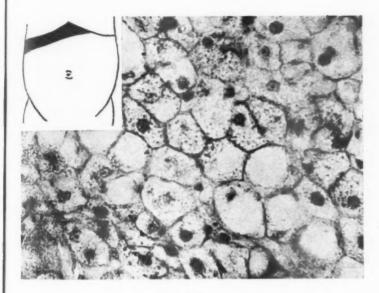


Fig. 2.

After about 3 months on the diet abundant in fat.

The liver extremely abundant in fat. Practically every liver cell contains fat, although in varying amounts. In the majority of the cells, however, the cytoplasm is quite filled with one or several enormous globules of fat. In others only a number of small globules are met with. The flattened nucleus is found in the peripheral parts of the cell, squeezed between the fat and the wall of the cell.

In all the cells glycogen is met with in the form of beautifully carminestained specks and laminae. In the fatty cells the glycogen is found in the form of a thin coat covering the globules of fat. In the cells with less fat there is more abundant glycogen.

Secretion granulae (the preliminary stages of the gall) are seen in all the cells, though in scanty amounts. As a rule the strikingly fine granulae are accumulated in the periphery of the cells.

After 47 days on a normal diet.

Still an abundance of fat, although not so much as on the previous occasion. A number of cells contain one or several large globules of fat, completely filling out the liver cells, though no definite localization of the

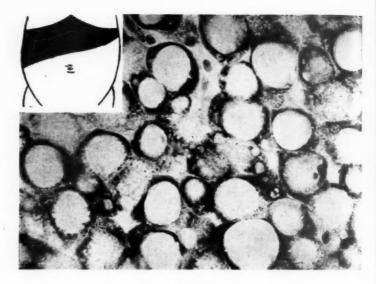


Fig. 3.

fat-containing cells within the lobuli can be traced. Other cells again contain smaller globules of fat or are entirely free of fat.

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Glycogen is met with in abundance in all the cells, except in those abundant in fat, where it is found in a thin layer between the globules of fat and the walls of the cells.

Secretion granulae are only found in scanty amounts in all the liver cells. Within a small area the parenchyma exhibits signs of degeneration, with liver cells in which strikingly small irregular nuclei and scanty amounts of fat and glycogen in the cytoplasm occur.

After 28 days on a diet abundant in fat.

The picture is now entirely changed. All the liver cells contain fat, though in varying amounts. The great majority of the cells are entirely filled by one or two large globules of fat. In some cells a varying number of small globules of fat are found.

Glycogen is found in all the cells, although in scanty amounts. Secretion granulae are also met with in appreciable numbers and as a rule only in the periphery of the cells.

The picture of the liver punctate is that of a very over-fatted liver, apparently poor in glycogen.

The findings in punctate III are in complete agreement with the results of the examination of punctate I.

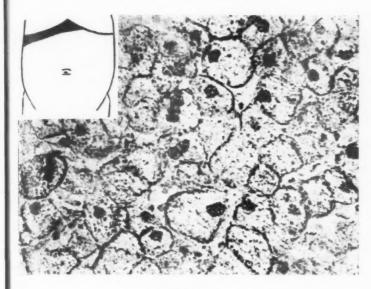


Fig. 4.

After 47 days on a normal diet.

Only occasional liver cells contain small globules of fat. The fatcontaining cells have no definite localization within the lobuli. In all the cells within the lobuli of the liver there is an abundance of glycogen completely filling out the cytoplasm. On the other hand, within the liver cells only sparse secretion granulae are met with, which as a rule are only found in the periphery of the cells in the neighbourhood of the gall capillaries.

The punctate exhibits the picture of a normal liver, abundant in glycogen and poor in secretion granulae and fat.

(The histological examinations were carried out by Docent HTALMAR HOLMGREN.)

It will probably emerge from the above description that the cause of the patient's fatty liver was not an acute or chronic infection, anemia or any sort of poisoning, but must have been of an alimentary nature.

A great many of the diets which were given to infants, especially some decades ago, were abundant in fat. In the early textbooks (e.g. Gerhardt, 1881, Henoch, 1887, Unger, 1901) it is pointed out, too, that fatty liver is fairly common, and to a certain extent physiological, in infancy. These investigations were based on autopsy material.

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There have been many experimental investigations on animals, and it has been emphasized in many quarters that fat appears in the liver after a meal containing an abundance of fat, and that the fat-content of the liver may rise to 40 %. However, in ordinary cases, the great variation in the fat-content is not caused by exogenously supplied fat, but the changes take place periodically, and fat is only deposited in the liver when there is an abundant supply of fat. Fatty livers have also been produced successfully by means of diets rich in proteins with a reduced supply of water. In this connection it should also be pointed out that there is a certain antagonism between the content of fat and the content of glycogen in the liver.

Conceptions as to the cause of fatty livers have been modified to some extent by the discovery of so-called lipothropic substances, for it has been found that under certain circumstances some substances can prevent the occurrence of fatty liver, and they are therefore called lipothropic. Among them are lecitin, and above all one of the chief constituents of the latter, namely, choline. Food poor in choline leads to fatty liver, and fatty liver can be prevented or cured with choline or lecitin. Certain protein substances also have a lipothropic effect, which is probably determined by their content of amino-acid methionine.

Another substance which has been considered to have a lipothropic effect is an extract of raw pancreatic juice, called lipocaic. It has not been elucidated whether this substance in itself has a lipothropic effect or is a catalyzing ferment which can hasten the binding of the choline in the lecitin molecule, and thus can have a lipothropic effect. However, lipocaic has been employed to eliminate the hepatomegalia which is not very unusual in diabetic children, and it has been successful in some cases (Grayzel and Radivin Rosenberg). In a case from the Norrtull Hospital Haglund tried the same thing with a preparation produced by Astra, but he was not successful.

The clinical application of the experimental results of the use

of lipothropic substances is still in its infancy. It is possible, however, that further investigations may yield, not only more definite information about the etiology of fatty livers and cirrhotic livers, but may possibly lead to a better conception of the causes of atherosclerosis.

In the above account of my own case I have not tried in any way to elucidate whether certain substances cause or cure fatty liver, but it has only been my object to show how easily and relatively quickly large amounts of fat can accumulate in the liver and how easily they can be made to disappear by means of a change in diet.

Discussion on Paper 25.

Räihä: In collaboration with cand. med. Alarotu I have performed some histological observations on the nervous tissue of pylorus in pylorospasm patients and would like to show some micro-photos.

The nervous tissue of these cases showed numerous gaps, the adjoining connective tissue was thickened, and inflammatory cells were found in the neighbourhoo dof the blood vessels. This points to lesions in this part of the nervous system which might possibly cause the spasm by preventing the normal evacuation reflexes of pylorus.

I have made some investigations which seem to indicate that pilocarpine promotes the evacuation reflex in the spastically contracted pylorus musculature.

Heikel: In connection with Dr. Vendel's paper on the evacuation of the stomach in infants I should like to mention some of the results noted by me in studying the effects of Pilocarpine on pylorospasm in infants. The investigations were based on data from the University Children's Clinic in Helsingfors, compiled in co-operation with Dr. C.-E. Rähä. I summarizing the results to-day I limit myself to the roentgenological aspect of the investigations. The method applied follows in the main the principles drawn up by Runström in 1939. 2 mg of pilocarpine were administered per os under x-ray control to patients suffering from clinically manifest pylorospasm. The results seem to indicate an increased peristalsis in the ventricle. In addition, a distinct dilatation was observed in the stenosed part of the ventricle, which was enlarged to twice its normal thickness, and the emptying of the stomach occurred noticeably sooner than without pilocarpine. Whether the dilatation occurs in muscularis or in muscularis mucosa? cannot be ascertained with cer-

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taintly. The cases hitherto examined are too few to allow of any farreaching conclusions being drawn, but they are interesting in so far as they indicate the possibility of a new medicinal line of attack upon pylorus-stenosis.

VENDEL: Dr. Răihā's report gives me occasion to demonstrate a curve in a case of pylorusspasm, with the object of illustrating how the evacuation coefficient may be used as an index to the progress of the morbid condition, or the advance of a cure or to the part played in the cure by a specific medicine.

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Sur

Sur la détermination du volume de sang chez l'enfant.

Par

P. KARLBERG et J. LIND.

Déscription d'une méthode non sanguine pour la détermination du volume de sang, bien apté à l'enfant. La méthode base sur les relations entre le teneur en monoxyde de carbon de l'air alvéolaire d'une part (en respirant de petites quantités de monoxyde de carbone) et le teneur du sang en carboxy-hémoglobine d'autre part. La méthode appliquée a été élaborée en principe par doc. T. SJÖSTRAND pour les adultes. La détermination de la concentration en monoxyde de carbone de l'air alvéolaire se faisait avec un carboxymètre d'une construction Suedoise, qui base sur l'oxydation catalytique du monoxyde de carbone par le hopcalit. (sensibilité 1: 1,000,000.)

Deux catégories d'enfants ont été examinées, d'une part des enfants au-dessous d'une année, d'autre part des enfants plus âgés au-dessus de 6 ans. Pour les enfants plus âgées on a utilisé la même méthode que SJÖSTRAND a appliqué aux adultes. L'individu à examiner doit respirer dans un système fermé avec de l'oxygène avec lequel on a mélangé de petites quantités de monoxyde de carbone. Pour les nourissons, une méthode spéciale a été élaborée, d'apres laquelle l'enfant même était placé dans le système fermé. Sur les nourissons 16 déterminations ont été faites, dont 12 en

double, et sur les enfants plus agés 25, dont 20 en double, avec une précision de \pm 7 % et \pm 5 % respectivement. Une correlation apparente se montrait au poids de corps et à la surface du corps. Les dates du volume de sang ainsi déterminées étaient du même ordre de grandeur que celles trouvées autrefois avec d'autres méthodes.

A new Vitamin affecting Anæmia in growing animalorganisms.

By

E. &. M. VERMEHREN.

29.

The blood copper in anaemias of children.

By

STEN AXTRUP.

I shall preface the account I intend giving here of my own investigations with an extremely short summary of the literature touching on the blood copper and its importance in the organism.

The physiological occurrence of copper in the organism of both man and animals was quite an early discovery, and many speculations were made as to its significance. After the investigations into nutritional anaemias published by the Wisconsin school in 1928 1929, however, interest was concentrated largely on the importance of the copper in the formation of blood. The fact was that the experiment animals reacted with pronounced anaemia to diet poor in copper, and this anaemia could only be cured by the administration of copper in some form or other. Anaemia due to copper deficiency could therefore by induced experimentally in animals, But a copper deficiency disease characterised primarily by marked anaemia could also be demonstrated in quite a short time in animals living under natural conditions, though this disease only affected herbivores, grazing on particular pastures. The onset of the anaemia could be prevented by prophylactic copper dosage. The food of omnivorous animals, as also the mixed diet consumed by children and adults, contains copper in quantities that amply cover the need of it. No copper deficiency diseases were therefore to be expected from these categories, nor did they yield any symptoms attributable to lack of copper.

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It was found, however, that mother's milk and, even more, cow's milk was poor in copper, and it was therefore assumed that some of the infant anaemias, in particular the so-called nutritional types, came from a copper deficiency. Analyses of the liver, which is the bodily organ where most copper is stored, had admittedly shown that the newborn child started with very much liver copper and therefore had considerable reserves, but it was also known that the copper content of this organ gradually fell. A couple of cases of grave anaemia of infancy had even shown the copper content of the liver to be extremely low. This supported the assumption that infants could show a copper deficiency. This view was further borne out by numerous reports of successful therapy tests with copper, either by itself or in combination with iron, in children suffering from anaemia, particularly the nutritional type. The clinical reports did not all agree, however. A number of authors were led by their own experiments to doubt the importance of copper in anaemias of children. Another circumstance suggesting that copper deficiency is not responsible for the anaemias was that copper analyses of the blood of anaemic children. often yielded raised copper values. However, the investigations into the blood copper of children generally and infants in particular proved very few, nor had the material been treated with sufficient discrimination: for example, insufficient regard had been paid to infectious factors, which of course tend to raise the blood copper. There is no doubt that quite a number of the raised copper values obtained in anaemic conditions can be explained in this way.

Thus, the recorded data as to the importance of copper in haemopoiesis were contradictory.

The point was, then, to try to clarify this problem. The task ahead therefore took the following form: Using a pediatric material, to study the level of the blood copper both under normal conditions and in anaemic conditions, particularly in the lower ages. In view of the great tendency of premature children to deficiency diseases, a study of these latter should be especially useful to throw light on the question as to whether or not copper deficiency can arise. The initially often quite troublesome feeding with small quantities of milk should mean that these children are worse off

for copper supplies than other children, particularly as the milk diet of premature cases is often continued over a fairly long period.

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The material investigated by me — totalling 146 children — came, therefore, to consist largely of premature children and twins, which last can in many respects be equated to premature cases, though a number of other anaemic children were examined. In addition, 64 children of different ages were studied as normal and comparison material. The greater part of the material came from the Pediatric Clinic in Lund.

The method used in the copper determinations was one outlined in 1941 by Holmberg. This method, which is based on Callan and Henderson's sodium diethylditiocarbamate reaction, is a macro-method but was adapted for micro-determination. The determinations were made in whole blood and on capillary blood from the finger-tip.

Investigation of the normal material, which consisted of full-term, healthy, non-anaemic children aged 1 week—13 years, showed the copper values to be about 116 γ %, i.e. the same normal value that most modern investigators have given for adults. In this material one value has been taken from each individual.

The procedure was different with the premature and twin material, 120 children in all. Here the individuals were followed up with as regular determinations as possible from shortly after birth to about 6 months of age, the customary blood tests being made at the same time. In this material the copper values were about 107 γ % without either rising or falling, although, true to type, quite severe anaemia developed. Thus, premature children show no difference from full-term children as regards the copper content of the blood during the first half-year of life. The premature anaemia during this period, therefore, can hardly be attributed to a copper deficiency.

To test out whether there was not, all the same, a lowered copper content due to copper deficiency, part of the material was treated perorally with copper in the form of copper sulphate, two cases with extremely low copper values being included. However, no permanent rise in the copper level was obtained, providing further support to the view that copper deficiency cannot lie

behind the anaemia of the premature. Nor had the copper treatment any noticeable effect on either the haemoglobin on the red blood cells in this material, not even in the cases with the low values, despite longcontinued and intensive copper therapy. When iron treatment was commenced after the copper treatment, there was a rapid rise of Hb and the red blood cells after a short period.

— In order to discover if the copper stimulated the iron in its action, 9 pairs of twins were treated with copper and iron in such a way that the one twin of a pair was given copper during a period while the other received no treatment. Both of them were then treated with iron. But no difference could be seen. The twin receiving only iron reacted just as quickly as the one previously treated with copper.

Besides the premature children followed during the first 6 months of life, a study was also made of a number of anaemic children aged 6 months — 2 years, i.e. the age where the so-called nutritional anaemias are commonest. The 17 investigated children included a number who could doubtless be classified as cases of nutritional anaemia, since they had been kept on a one-sided milk diet for a long time at home; but the material also contains a number of cases where infection entered the picture as a factor

promoting anaemia.

These children, too, were found to have blood copper values which kept round the same level as that of the full-term non-anaemic children, and there was no general fall of the blood copper values, though this should have been the case if copper deficiency had been present. It is true that these cases, too, included two with really low blood copper values, but these did not react to copper treatment with any permanent rise, either. Nor could any particularly raised values be recorded except where the patient was undergoing an infection or had recently been suffering from some infectious complaint. Even the patients with low blood copper might, on infection, react with repeated and pronounced rises of the copper content — another indication that the copper supply of the body was not exhausted. It is unlikely, then, that these anaemias are due to a copper deficiency. However, in certain cases the copper seems able to stimulate haemopoiesis even when

the organism appears sufficiently supplied with copper. That is to say, when this last material was treated with copper and iron, it was possible to register an effect from the copper treatment in a couple of cases where the copper was given after the iron treatment had commenced. These were two cases of very protracted anaemia, which reacted very badly to iron treatment. When copper was commenced there was a distinct and fairly long-continued rise of reticulocytes, though only reflected in a very slow and slight improvement of the anaemia. In protracted anaemias of this kind, reacting poorly to iron, it may therefore be advisable to try copper together with the iron medication. Usually, however—as is universally evidenced — these so-called nutritional anaemias react excellently to iron therapy. There should therefore be hardly any reason to make a special addition of copper to the iron preparations.

As a general conclusion, then, it can be stated that there is no need to fear a copper deficiency in infants, although they may offer some of the conditions for such a state. They have sufficient reserves to cope with their copper requirements, even if the supply is small. The blood copper seems to be governed by endogenous factors and apparently remains constant whether the individual in question is suffering from anaemia or not, but it is extremely labile in the presence of infection. It should only be justifiable to use copper as a therapeutic for anaemia in certain individual cases as a last resort, when iron therapy has had a bad effect.

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For detailed bibliography, see:

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30.

Eosinophilia Leukæmoides.

By

OLGA IMERSLUND.

Cases described as eosinophilia leukæmoides and eosinophilic leukemia belong to heterogenous groups of diseases. The common features are hyperleukocytosis and eosinophilia with mainly mature eosinophilic cells. Otherwise they exhibit widely differing symptoms and signs. Some cases showing these blood changes and also certain skin eruptions will be described. Only a few cases showing this combination have been reviewed earlier.

Case 1. Girl, born 14. 1. 43. Birth weight 3500 g.

Nothing relevant in the family history or the patients own history till she was 10 months of age. 9 months old she was put on ordinary mixed diet. One month later a small-spotted itching exanthema appeared, starting on the buttocks and spreading to the rest of the body. When the child was given eggs, the exanthema grew werse. She also had anorexia and there was little increase in weight. 1½ years old, her condition grew worse by the appearance of constantly recurring furuncles.

When she came under observation a little later, she had just recovered from acute pyelitis and bronchitis. The general condition was then very poor. Weight 8.4 kg. Length 78 cm. She had an exanthema all over the body, least marked in the face. The skin was diffusely crythematous and thickened, especially behind the knees, where it was leathery. In palms and soles there was large-scaled desquamation, in other parts fine desquamation. Growth of hair was sparse. There were rhagades at the angles of the mouth and other places. She had general adenitis, freely movable glands up to the size of hazel-nuts. The liver was palpable two finger shreadths below the costal margin, firm. The spleen could not be felt.

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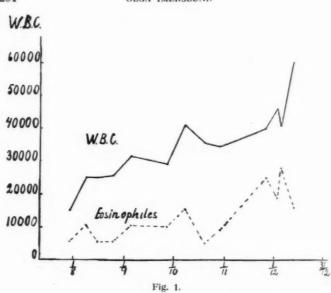
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Skin tests showed hypersensibility for several food articles. X-ray showed blurring of the left maxillary sinus. Biopsy of a gland showed infiltration of mature eosinophilic leukocytes. Biopsi of skin showed a moderate infiltration of lymphocytes and some macrophages, no infiltration of eosinophilic cells. During the first few weeks in hospital there occurred with few days interval, exaggeration of the exanthema, which became redder, angrylooking and itching. At the same time there was vomiting, diarrhoea and weight fall and also a rise of temperature. Gradually these periods became more infrequent. She kept on developing fresh furuncles which disappeared under penicillin treatment. She developed ac. rhinopharyngitis several times, and shortly before discharge from hospital, whooping cough.

The appetite was variable. Some days the intake was fairly good, but there was no tendency to wt. increase, or to changes in the skin or in the condition generally, even after she was put on a diet towards which she showed no hypersensibility neither by oral ingestion nor by skin tests. For about a week she was given breast milk only, but did not improve even then. After 4 months in hospital the condition was mainly unchanged. The weight was 2 hg less than when she was admitted. Two years old, she died suddenly during a fit of whooping cough.

No post mortem was performed.

Case 2. Boy, born 3. 1. 46.

An uncle suffers from asthma, otherwise healthy family.

The birth weight was 3300 g. The child was breast fed. Aged 3 weeks he developed an exanthema on the scalp and the cheeks, spreading to the whole body. He showed normal development till he was 3 months old when he became listless, quiet, and showed little wt. increase although control showed that the mother had sufficient milk. The stools became frequent and loose, sometimes watery.

When he came under observation 3 months old, he was thin and the general condition was very poor. Weight 3700 g. There was some intertrigo in the skin folds. He had a general exanthema very similar to that of the first patient. There was less redness and less desquamation, but there was some exudation. The skin was thickened, mostly behind the knees where it was of leathery consistence. There were fissures, and the exanthema was very itchy. He had a general adenitis of the same character as in case 1. The liver could be felt just under the costal margin. A slight rise of temperature could possibly be explained by a light pharyngitis. There was little tendency to wt. increase.

Biopsy of skin showed hyperkeratosis, no infiltration of eosinophilic cells. Biopsy of gland showed infiltration with mature eosinophilic leukocytes. Skin tests showed hypersensibility towards egg albumen. There was also a decrease of plasma proteins.

Case 3. Girl, born 8. 2. 1946.

Healthy family. Birth weight 3590 g. She was breast fed with additional cow's milk. 2 days old she presented an exanthema consisting of small red spots over the whole body. She came under observation 14 days old. The wt. was then 3100 g. The general condition was good.

Over the whole body except palms and soles there was an exanthema consisting of erythematous areas, small papules, papulopustules and pustules, some of them covered with crusts, arranged in groups and stripes. Liver and spleen were just palpable. There was no adenitis. She was put on breast milk and increased slowly in weight. The exanthema later showed more vesicles, and the group arrangement became more marked. There were constantly fresh eruptions with few day's interval, but never any itching. Skin tests with different food articles showed no hypersensibility. Biopsy of skin showed infiltration with mature eosinophilic leukocytes.

The leukocyte count has in these three cases repeatedly been over 25000. The first patient whose symptoms and signs were most severe, had as a rule more than 40,000 the last two months. During the first stage of her whooping cough the leukocyte count was 60,900. She had up to 63 % eosinophiles, i.e. more than 27,000 eosinophilic cells per cm³. In all cases the eosinophilic leukocytes have been mainly mature forms, sometimes with so-called pseudomature structure i.e. hypersegmented

nuclei and vacuoles or faintly bluish-stained areas in the cytoplasm. as reported earlier in cases of hyperleukocytosis with eosinophilia. On a few occasions blood examination has showed shift to the left. Apart from this there has been no marked deviation from the normal. No anemia or thrombopenia. No bleeding tendency. Tibia puncture has in all cases shown increase in eosinophilic cells, mostly the mature forms, which had an appearance similar to those of the peripheral blood.

The examination has otherwise not shown anything particular. By examination of the relatives no eosinophilia has been found.

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Clinically there is such a striking similarity between the first two patients that one gets the impression of a special disease entity, characterised by dystrophia with little tendency to wt. increase in spite of adequate diet, adenitis with infiltration of eosinophilic leukocytes, and markedly thickened, leathery skin. Besides, the syndrome occurs in both cases in children who show allergic reactions. The skin changes might be called eczematous, but the excessively thickened skin differs from the usual appearance of eczemas in infants and small children. Moreover, in the first case no papulovesicles which are the primary elements in eczemas were found. The cases are reminiscent of Hill's atopic erythrodermia.

The last case seems to belong to a different group of diseases. The general symptoms and signs have been less marked. There was no dystrophia, no swelling of glands and the skin eruptions had a different appearance and showed infiltration with cosino-philic cells.

Possibly this is a case of dermatitis herpetiformis which may occur early in infancy.

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31.

The development of the ossific centres in some diseases in early childhood.

By

OLLE ELGENMARK.

During the years I have been studying the normal development of the ossific centres in infancy and childhood, I have assembled a number of cases showing an abnormal development. The material is not large, but it is sufficient to give some idea of the importance of studying the ossification process in the case of disturbances in growth and development of the body.

As a basis for the judgement of this pathologic material I have used the tables which I have compiled to represent the normal ossific centre development; These are to be found in Acta Paediatrica, vol. XXXIII, Supplement 1 (1946). These tables were worked out in accordance with a method indicated by the Americans Sontag, SNELL and ANDERSON (1939). Earlier authors believed it was possible to draw fairly definite conclusions regarding the development of the ossific centres in the skeleton as a whole on the basis of the development in one single ossification area, usually the hand and wrist and in some cases also in the foot and ankle. The range variability in the time of appearance of the individual ossific centres is so wide, however, that this method is not satisfactory. Furthermore, in my investigations on the ossific centres I have shown that, statistically speaking, the correlation between the development of the different centres is not so absolute that definite conclusions can be drawn from the date

of appearance of one centre as to the possible dates for the appearance of others. Thus, in order to obtain a fairly correct view of the degree of maturity of the ossific centres it is necessary to study a larger number of them, and I have therefore included all the centres in the extremities of the one side of the body, 68 in number, in every examination. All ossific centres found were added together and the figure thus obtained was regarded as a standard for the development of the ossific centres at the examination in question.

In the statistical calculations it soon proved that the ossific centres had a stronger correlation to height than to age. Normal tables were therefore drawn up with respect to both age and height, and I suggested that at routine examinations it is more advisable to use the tables relating to height, and in dubious cases, to use as well the tables making a correlation with age.

It was also found necessary to make a distinction between boys and girls, because in the latter the development was in advance of that of the boys during the whole age period examined. Of special interest in this context, is the rapid increase in the number of ossific centres which in girls occur at a height of 70 cm and at an age of 10 months and which has no analogy in boys.

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With the assistance of these normal tables, the development of the ossific centres has been studied in a number of diseases. Greatest interest was attached to such diseases as are known to influence the normal development of the ossific centres. Through a study of these diseases, it is possible to form an idea of the value of the normal tables. My cases have been assembled in tables, the first of which contains disturbances in the growth such as hypothyreosis, suspected cases of this disease, and such patients as were characterized as cases of delayed development after isolated symptoms of physical or psychical immaturity had caused them to present themselves for examination.

Table 1 shows that in individuals with signs of hypothyrcosis the ossific centre development is below the value 1 a as compared with the normal tables for height and age. It is difficult to fix an absolute lower limit under which the development of the ossific centres can be said to be pathologic. By comparing the clinical

Table 1. Cases of disturbances in growth.

Case	Sex		V=	Age		year	Clin. diagnosis	Number of os. centres	Numb o.c. ac	er of	Comments	
no.		m=month			or	nth		N o a	height age			
1	g.				5	m	Myxedema	4	8±2	10±2	Death	
1	g.	1	y	7	3	3	Hypothyreosis	10	19±4	29±9	Treatm.	Thy
		1	1		9	9		12	41±9	41±8		
		4	1	Þ	6			62	64±2	63±2		
3	b.							7		12±3		
		1	. 1		2	9		14	20±6	14±3		
		1	1		6	9		19	23±8	20±5		
4	b.	1	. 1	•	2	9	Hypothyreosis?	13	20±5	20±6		
		1	1		9	9		21	25±7	25±8		
5	g.	1		1	11		,	13	28±8	23±7		
				1	12			20	28+8	25±8		
6	b.	5	1		5	9		12	20±5	23±8	9	
7	g.	2	. 1	1	10			11	41±9	56±8	9	
8	b.				6	9		8	12±2	11±2		
9	b.	1	1		6	9		12	20±5	23±8	9	
		5			3			29	35±7	17±8		
10	b.				2	9	,	8	7±	6±2		
11	b.				4	9	,	8	9 ± 2	9±3		
12	b.	1			2	3	,	8	7±2	6±2		
13	b.	2	3)	7	9	,	32	45±8	40±8		
14	b.	1	8	,	5	9		11	20+5	23±8	9	
15	b.				1		,	6	5+1	6±2		
		1			5	9		10	9+2			
16	b.				6	3	,	10		11±2		
		1	,					15		16+5		
17	g.				8	9	(obstipation)	12		15±3		
-	0.					9	(====,	15		16±2		
18	b.	1	9		6		Delayed developm.	15		23±8	,	
		2					(Does not walk, teeth 4/4)	26		25±8		
19	b.	1 -	8		9	9	Delayed developm. (Bodily con- dition good. Dull. Cannot					
							walk. Teeth 4/4)	14	35 + 7	25±8		
20	b.	2	,		7		Delayed developm.?	35		44±8		
		-			•		Dry skin, slow movements. speaks badly)	00	1010	1110		
21	g.				4	3	Del. devel? Eyes do not fix, hands do not grasp. Body well-covered	4	8±2	8±2		
22	b.	1			5	9	Del. devel. (Teeth 4/4, cannot stand. Dull)	15	20±5	23±8		
23	b.	1		1	1	9	Psychich debility?	29	35±7	32±9		

^{14 —} Acta pædiatrica. Vol. XXXV.

findings with the corresponding development of the ossific centres, I have been able to set the boderline for normal development to 1 α . In cases with clinically uncertain hypothyreosis and in patients with some isolated sign of delayed development several showed, as appears from the table, a development under 1 α and were thus considered to be pathologic. These cases were treated with thyreoid hormone and in a short time the number of ossific centres became normal and the clinical status also improved. To a certain extent this indicates that in these cases the development was delayed and it supports the view that the lower normal value is 1 α .

The question arises as to what age can be considered the earliest from which X-ray examination of the ossific centres will indicate delayed development. None of the cases I have examined showed signs of delayed skeletal development before the age of 4 months. All the infants up to this age, were breast-fed babies and it is possible that the thyreoid hormone in the breast milk had sufficed to keep the symptoms away. From the age of 4 months and onwards, pathologic conditions in ossific centre development were observed in several cases. The material is, however, too small to permit any definite conclusions to be drawn regarding abnormalities in the ossification at this age. Nor is it possible to decide if it is a mere coincidence that of the 23 cases of delayed development 17 were boys and only 6 girls.

Thus it is possible, by means of my normal tables, to form an idea of whether the bone development is normal or delayed. It is of interest to ascertain to what extent similar conclusions can be drawn through a study of the skeleton of the hand and the wrist alone, the method previously employed by most investigators. To decide this, I studied the ossific centres of the hand and wrist, and in addition to this I also examined the foot and ankle. As each ossific centre appeared it was compared with the date of appearance of that particular centre noted in the normal tables. There is such variation in the normal development that, as regards the wrist, the date of appearance of the centres for the capitatum and hamatum is at 9 and 10 months, respectively, while the latest date is at almost 5 years for the triquetrum and lunatum. To determine the degree of skeletal maturity in general

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on basis of the findings in the wrist is under such circumstances impossible.

The ossific centres in the hand show the same wide range of variability in development. Thus, in none of the cases examined, was it possible to form an idea of the skeletal development as a whole from observations on the ossific centres in hand and wrist. My case of myxedema, in which the centre for the capitatum was present but the bone development in other respect showed evidence of a considerable delay in the maturity of the centres, is interesting. If the foot and ankle are also included there are better possibilities for judging the general development. I found sufficient deviations in the ossific centres in these areas to be able to establish that the development was pathologic in a number of cases. It is questionable therefore, whether there is any need to examine in addition other small ossification areas such as knee, hip, elbow and shoulder. In some of the cases examined, however, it was not possible to diagnose delayed development without these areas. In case 9, for instance, there was no sign of the centre for the proximal epiphysis of the femur, which is present in all normal individualls at the age of 10 months, or of the centre for the coracoid process, which appears between the ages of 1 and 26 months. In case 21 the ossific centres for the proximal epiphysis of the tibia and the proximal medial epiphysis of the humerus had not appeared, this finding being the reason for the diagnosis of delayed development of the ossific centres. There are more examples but these are sufficient to prove my point.

Thus, it is undeinable that the method for studying ossific centre development described here is more advantageous than earlier methods.

The next table, no. 2, shows some cases of mongolism and other abnormities presenting features of interest as regards the development of ossific centres.

No case of mongolism had delayed skeletal development. The development was normal also in the other congenital abnormities, including a few cases of extreme hydrocephalus.

An interesting feature is that the two cases with cryptorchism both showed such marked retardation in the development of the

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Table 2.

Cases of mongolism and other abnormities.

Case no.	Sex	Age y=year	Clin. diagnosis	Number of os. centres		oss. c.	Comments		
110.		m=month		No o	height	age			
1	b.	1 m	Mongolism	4	3±1	5±2	Death		
		8 .		10	9±2	13±2	Death		
2	g.	2 y		34	41±9	47±7			
3	b.	5 .		8	9±2	10±2			
4	b.	7 .		11	12±2	12±2			
5	b.	2 .		9	7±2	6±2			
6	b.	2 . 2 .		30	35±7	37±5			
7	g.	1 .		25	28±5	25±8			
8	g.	10 •	Hydrocephalus	10	14±2	18±4	Circumference of		
							head 57 cm		
9	b.	4 .		6	9±2	9±3	 81 ₁		
		10 •	1	10	12±2	15±3	 59 ₁		
10	g.	8 .		14	14±2	15±3	 54 ₁		
11	g.	1 . 6 .	,	30	29±8	38±9	—→ 58 ·		
12	g.	1 .	Vitium cordis	5	6±2	5±2			
13	b.	1 . 4 .		12	14±2	20±3			
14	g.	1 . 9 .		38	41±9	41±9			
15	g.	2 . 6 .		49	48±7	53±6			
16	b.	1 . 7 .	Cryptorchism	16	25±7	25±8			
		2 .		22	34±7	32 ± 9			
		2 * 10 *		27	43±5	44 ± 5			
17	b.	1 . 8 .		16	25±6	25±8			
18	-	4 + 11 +	Hermaphroditis	66	43±6	62 ± 3			
19	g.	1 . 6 .	Large mammae	44	29±8	33±9			

ossific centres, and also that a hermaphrodite aged 5 years showed skeletal development more closely resembling that of a girl despite the fact that the appearance was more like that of a boy and that the infant had been given a boy's name. To determine the sex a trial laparotomy was done, and it was found that both testes and ovaries were lacking. The only thing to be seen was a spool-shaped formation on one side of the midline, which might have been either an epididymis or possibly a rudimentary uterus.

In this context it may be pointed out that the previously mentioned difference between ossific centre development in boys

Table 3. Cases of nutritional disturbances.

Case	Sex	Age y=year	Clin. diagnosis	No. of oss. centres	No. of acc.		Comments		
no.		m=month			height	age			
1	b.	1 y 3 m	Celiac disease	12	14±3	20+6			
		1 + 4 +		12	14±3				
		1 , 6 ,		12	14+3				
2	b.	2 , 9 ,	3 9-	16	20+5	44+5			
		4 , 9 ,		49	45±8	62±3			
3	g.	3 . 7 .	, ,	30	41+9	61+6			
		4 .		43	48+7	61+6			
4	b.	3 »		19	25+7	48±6			
		5 »		31	43+6	-			
5	g.	5 .	, ,	49	59±3	64 +2			
		5 . 10 .		61	61±3	_			
6	b.	2 .	, ,	13	14+3	32 + 9			
		2 . 3 .		15	19士5	37±5			
7	b.	1 . 5 .	, ,	14	20±5				
		1 . 9 .		20	25±7	25±8			
8	g.	1 . 5 .		18	18+4	33±9			
9	g.	5 ,	Dystrophia	6	6+2	10±2			
		6 ,		9	8±2	11±2			
		8 »		9	8±2	15±3			
10	b.	1 . 5 .	Acute recurrent	12	14+3	23±8	Recurring		
			enterocolitis				symptoms 1 y		
11	b	2 . 3 .		39	35±7	49±7			
12	g.	1 > 4>	Acute recurrent dyspepsia	14	18±4				
13	g.	1 + 5 +	Acute recurrent dyspepsia	13	14±3	23±8			
14	b.	2 * 5 *	Fermentative dyspepsia	34	35±7	49±7	On diet for months		
15	b.	1 . 7 .	Fermentative dyspepsia	21	20±5	49±7	On diet for months		

and girls during the first few years of life ought to give a certain amount of guidance as to the sex in hermaphroditism.

The last case in table 2 is a girl, 1 year and 6 months old, who had definitely enlarged mammae without any other symptoms of abnormal development. There was a greater number of ossific centres in this child than is normally the case, a fact which may conceivably have had a causative connection and therefore is of great interest.

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Rickets was studied in 16 cases the diagnosis having first been verified by X-ray examination. It was found that only in the advanced active forms of rickets is the appearance of the ossific centres delayed.

Nutritional disturbances can also produce disturbances in the development of the ossific centres as may be seen from table 3.

It has earlier been indicated that dwarfism can occur in celiac disease. In the 8 individuals with this disease which I have examined the degree of skeletal maturity corresponded to that of the healthy child of the same height, while on the contrary, it was greatly delayed in relation to age. The same seems to be the case in chronic intestinal catarrhs and in recurrent acute intestinal infections.

My aim in the present report has been to demonstrate the usefulness of my normal standard tables of ossific centre development for the X-ray diagnosis of skeletal maturity. At the same time I have endeavoured to point out that it is not possible, as has been done by previous investigators, to draw hard and fast conclusions as to the degree of the skeletal maturity as a whole from the observations on isolated ossification areas such as hand and wrist.

Summary.

It seems to be possible, by means of this type of examination in the early years of life, to gain some knowledge of disturbances in skeletal development, as well as the degree of this development.

Discussion on Papers 27-30.

Agren: In connection with the interesting communication we have just heard I should like to mention that the formula for folic acid has now been published. Several factors indicate that one may fairly safely rule out the possibility of folic acid being identical with the anti-anaemic liver factor.

JALAVISTO: Following Dr. KARLBERG's paper I should be interested to learn whether the viewpoint expounded below has been considered in studies relating to the blood volume in children.

In view of the fact that CO is absorbed by the haemoglobin as well as by the myoglobin, which is regarded as a source of error in tests performed by the CO-methods, the blood volume values obtained by this procedure are commonly held to be too high. Dr. KARLBERG's curves show that the correlation between the blood volume values registered by the method reviewed and the weight of the children is fairly good. Some specific values are, however, definitely outside the regression line. Since it is known that exercise increases the myoglobin content in the muscles, it is conceivable that the values which are too high in relation to the body weight might apply to particularly active and muscular children The haemoglobin store in such children is likely to be higher than in patients who have been inactive, for instance bedridden, for a long time. Conversely, one would expect to find lower values in weak children than in children possessing average strength. Of course, it might be argued that the reclining position in bed and the inactivity are in themselves liable to bring about a decrease in the blood volume. By means of tests carried out by several different methods systematically considering the activity and muscular strength of the children, it should be possible to ascertain the part played by the myoglobin in estimations of the blood volume by the CO-methods. If the myoglobin plays an important part, consistent results would be obtained only in respect of weak children with poorly developed muscles, whereas the results pertaining to strong children would be inconsistent.

As the myoglobin content is the same irrespective of whether the muscle is contracted or not, (and a muscle section, although not at work, is not entirely cut off from the circulation (added to proof-with) a comparison between tests performed on the same person muscles at rest and at work respectively would hardly be of any value.

Vahlquist: Dr. Vermehren has carried out his investigations on pigs. Other investigators have earlier emphasized that the anaemia which is fairly common in these animals in the first stages of their existence is of the iron deficiency type. In view of this it is remarkable that a preparation which does not contain iron is capable of staving off the anaemia and maintaining the Hb-values on a satisfactory level. It may reasonably be contended that the demonstrated effect is due to either the new preparation favouring the absorption of iron from the food or the mobilization of iron from some tissue depot. It would be interesting to learn whether Dr. Vermehren has carried out any experiments tending to elucidate this point, and also whether the new preparation has proved to have the same effect from a curative as well as from a prophylactic point of view.

RANTASALO: At the Hospital for Infectious Diseases in Helsinki we had recently as an in-patient a girl aged 17, who had previously suffered for six months from slight attacks of asthma, symptoms of which were absent, however, during her stay in hospital. On admission, she had for a couple of weeks previously had pains in her ankles, spells of fever and intermittently insensitive patches on her feet. Spleen, liver and lymphalic glands = 0. Skin tests did not reveal any particular sensibility. The blood contained 43.600 leukocytes, 84.5 per cent being eosinophils. Corpuscles of blood and medulla were ripe and normal. Treatments with sulpha-, penicillin- and vitaminepreparations proved ineffective, and the same condition persisted during three weeks. A course of sulphur treatment, allered, was then started, whereby the blood picture rapidly improved. Six months after the onset of the illness, leukocytes were 7500 and the eosinophil percentage 12.5.

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32.

Experiences from operated cases of patent ductus arteriosus.

By

EDGAR MANNHEIMER.

It has been possible, owing to improved diagnosis and surgery. to bring about a radical cure of no small percentage of congenital heart malformations. This is the outcome of advances made during the last eight years as regards the treatment of these congenital defects. In 1938, Gross undertook the first successful operation of patent ductus Botalli, After him, a varying number of similar operations have been carried out in most countries. In Sweden, the number of cases operated upon by Crafoord is now seventyfive, Crafoord performed his first operation in May 1941. He was also the first in the world (1944) to operate upon cases of coarctation of the aorta, with extirpation of the stenosed part and restoring of the aorta to its normal condition by means of end to end suture, resulting in, as far as has been possible to determine, complete health. In 1945, a series of successful operations of the morbus ceruleus cases were reported from America. At HELEN TAUSSIG'S suggestion, BLALOCK (1945) made about forty operations on children suffering from tetralogy of Fallot and isolated pulmonary stenoses. Only cases with a low pulmonary pressure and an insufficient blood supply to the lungs were operated upon. The intervention consisted of anastomosis between an artery, usually the subclavian artery and the pulmonary artery distally of the stenosis. In this way, an artificial ductus arteriosus was constructed,

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so to speak, thereby increasing the supply of blood to the lungs. There can be no talk of a restitutio ad integrum in this connection. However, a pronounced improvement took place in the majority of these cases and the cyanosis decreased. In several instances, the oxygen saturation of the blood rose from 30—40 per cent before operation to 80 per cent or more after. Also the function of the heart improved, and patients with a severe insufficiency were able to move about freely after the intervention.

By this introduction I have wished to make clear that we are at the beginning of a new epoch concerning the treatment of congenital heart disease. This, in turn, places increased demands on our diagnostic ability. A satisfactory result can only be achieved by a close cooperation between the pediatrician, interested in cardiology, or the doctor of internal medicine, on the one hand, and the surgeon specialized in thoracic surgery, on the other.

Five years have now elapsed since Crafoord performed his first patent ductus arteriosus operation. It may, therefore, be regarded as appropriate to present a report of the results from follow-up cases. Before doing so, the diagnosis and the surgical indications will be briefly stated. For further details, reference may be had to a work by Crafoord, Mannheimer, and Wiklund (1944).

The diagnosis of patent ductus Botalli is almost exclusively based on the continuous murmur. This murmur, which was discovered as early as in 1900 by Gibson, differs from the systolic, as well as the various diastolic murmurs, in the following respects. It starts in the middle of systole, attains its crescendo approximately at the second sound, continuing for the greater part of diastole. It represents, in the majority of cases, one of the strongest murmurs and may often be auscultated with a stethoscope on top of the bedspread. It is fairly easy to recognize owing to its characteristic sound quality. However, the diagnosis is established most simply by means of a phonocardiographic examination, the forementioned distinctive features being registrable in the curve. The murmur has its punctum maximum over the pulmonary artery in all cases. This should be clearly borne in mind, since continuous murmurs exist with a different localization. It is a sign

of an arteriovenous communication, and the phenomenon is known to occur at peripheral arteriovenous aneurysm, over a thyroid in a Basedow case, at certain rare congenital defects where the murmur is perceived maximally over the aorta or in the fourth intercostal space to the left of the sternum (congenital arteriovenous aneurysm and patent truncus communis), at auscultation over the fontanel of infants, and, finally, as a normal sound phenomenon on the lateral part of the neck, the so-called venous hum in the neck.

Apart from the cardinal symptom, i.e. the continuous murmur, the following may also be stated regarding the diagnosis. Since a thrill is merely an expression of a murmur of such strength as to render palpable the thoracic vibrations produced by it, it follows from what has already been mentioned that most of the cases have a distinct thrill over the pulmonary orifice. Gerhard's dullness is noted in several instances but is sometimes lacking. The same applies to the large amplitude of the blood pressure which occurs, though irregularly. The Röntgen examination, as a rule, discloses an enlargement of the left ventricle due to the extra work caused by the shunt. The pronounced pulmonary arch, to which is attributed such great significance in some quarters, is manifested in a certain number of cases, but by no means in all. In addition, it occurs in several other congenital diseases of the heart. Sometimes the röntgenogram is normal. A normal electrocardiogram is typical of this disease, indicating an extracardiac localization of the defect. At other times, signs of a secondary myocardial damage are seen in the electrocardiogram.

To summarize, the key to the diagnosis may be said to lie in the continous murmur and its punctum maximum over the pulmonary orifice. The phonocardiographic examination will verify the diagnosis. It is, moreover, principally thanks to this method that all the cases sent to operation from The Crown-princess Lovisa's Children's Hospital during the past years have been found to have a correct diagnosis.

The surgical indications are variously interpreted in different quarters. Hubbard (1939), for instance, has divided the cases into compensated and decompensated ones, suggesting operation

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only of the patients belonging to the latter group. After having consulted CRAFOORD, we have adopted the method of regarding all cases with this diagnosis as indicating operation, or that all definite cases of isolated patent ductus arteriosus should be operated upon. This point of view finds support in the following observations which simultaneously disclose the fact that all cases of patent ductus arteriosus show a varying degree of cardiac dcompensation. Abbott (1937), and Bullock, Jones and Dolley (1940) demonstrated the much shorter period of life than is normal of persons suffering from patent ductus arteriosus. This is further borne out by the experience that the great majority of cases occur among children. This disease is a pediatric affection. It is rarely noticed by doctors of internal medicine. Abbott showed that the risk of endocarditis in the canal is considerable. In twentyeight of Abbott's ninety-two post-mortem cases this complication was the cause of death. Eppinger, Burwell and Gross (1941) found in their investigations that a large quantity of blood (i.e. 50-75 per cent of the total amount) passes through the shunt. This must involve, partly, a greater exertion on the part of the left ventricle and, partly, an insufficient supply of blood through the aorta. Finally, the important social indications for operation should not be overlooked. These patients with their marked continuous murmur are unable to obtain health certificates when applying for various situations and are, therefore, handicapped from a social point of view. It is not least for this reason that the patients themselves or their parents desire operation to be carried out.

Thus, the matter may be viewed as follows. All the isolated cases of patent ductus arteriosus have been suggested for operation. The aim is now, five years after the first surgical intervention of this kind in Sweden, to attempt to estimate the results. A period of observation of up to five years is, of course, not particularly long. However, the experiences gained may, perhaps, justify certain conclusions.

The number of cases from The Crown-princess Lovisa's Children's Hospital comprises operated cases as well as cases not yet subjected to treatment. The latter amount at present to about

Table 1.

Operation year	3-	8 yrs Q	9-1	4 yrs Q	> 1	4 yrs Q	₹ ð	otal Ç
1941	1	1				2	1	3
1942		1	1	1		1	1	3
1943	2	3	1	2			3	5
1944	1	1				1	1	2
1945	2	2	1	3			3	5
1946	1	1		3		1	1	5
Total	7	9	3	9	0	5	10	23

forty. These cases have not been included in this investigation since they cannot be considered to constitute a control group as regards operated cases. Most of them are waiting for operation or have not as yet attained the age (3—4 years) required, according to Crafoord, before undergoing a surgical intervention. I shall therefore limit myself to a brief account of the operated cases. The intervention has consisted of ligation or division of the ductus and primary suture.

Thirty-three of forty operated cases were afterexamined. The age distribution and the time of observation are illustrated in Table 1.

The time of observation exceeded 3 years in 16 cases. In accordance with earlier knowledge, girls are more often than boys the victims of this anomaly. More than half of the cases were operated upon before the age of ten years. In our opinion, children endure this intervention better the younger they are, down to about 3 or 4 years of age.

The mortality rate is restricted in the present material to one death. It concerns a girl of five years whose heart suddenly stopped beating after a perfectly normal operation. This happened in connection with the removal of the tube for the narcosis in the trachea. It was possible, by means of adrenalin, administered intracardially, to restore heart activity but the patient died, nevertheless, 48 hours after the intervention, probably owing to the cerebral injury caused by the interruption of the circulation to the brain. Apart

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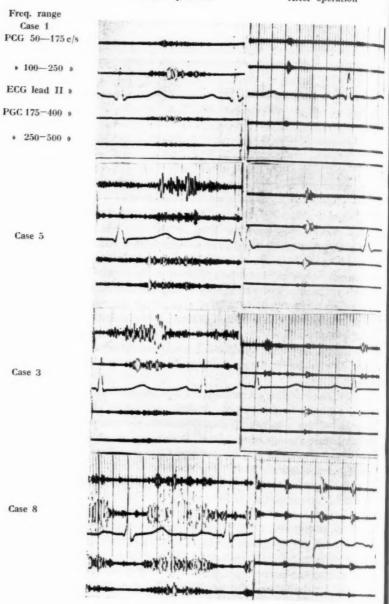


Fig. 1. Phonocardiogram of 4 cases before and after operation.

from this case, Crafoord reported another death (not included in our material) of an adult suffering from septic endocarditis in her ductus. which had been diagnosed prior to operation. Another three cases have been operated upon — all with good results. One of these cases, belongs to this after-examination group. It is a girl of ten years who was admitted in a very bad condition with a high temperature, positive blood culture, high sedimentation rate. Now, barely three months afterwards, she is altogether free from these symptoms. She was given pre-operative treatment with penicillin.

No recidivism has occurred, with the exception of the case of septic endocarditis which was fatal. Repeated phonocardiographic examinations performed post-operatively have verified this statement. Fig. 1 shows the phonocardiograms of four cases before and after operation.

Prior to operation, 8 of the 33 after-examined cases had cyanosis at exertion, 16 felt a shortness of breath at but slight exertion and 16 had considerably less strength than their comrades of the same age. These symptoms disappeared in all the cases, and the patients or their parents are able to testify to the great difference before and after the operation.

Several of the cases had earlier been pronounced as hopeless by their doctors. They were, furthermore, mentally backward, inter alia, owing to the anxiety of their parents, and not a small number of them disclosed other signs than those reported above of a bad general condition such as, pronounced anorexia, probable ischemic pains in the lower extremities, etc. The development after the operation was satisfactory in all cases but one. It has not been possible to distinguish between these children and their comrades as regards physicial or mental development. The exception is a boy of three years with infantilism, whose sell turcica was reduced, indicating the occurrence of a hormonal insufficiency.

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Good results can also be shown from a social point of view. For example, a girl of 18 years may be mentioned, who was denied employment at the Post Office before operation but has now, after the intervention, become permanently employed there.

The Röntgen examinations have throughout disclosed a decrease

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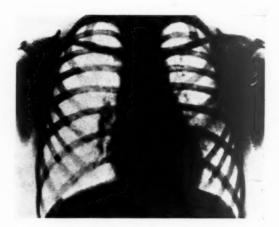
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Before the operation.



A few days after operation.

Fig. 2. Röntgen examination, girls 7 years. (380/39).

Table 2. Röntgen examinations.

Heart volume per m2 of body surface (according to Liljestrand, Lysholm, Nylin och Zachrisson 1939).

ECG no.	Before operation	After operation	
39/38	355	320	
68/39	460	345	
380/39	650	315	
481/39	470	435	
989/39	305	315	
701/40	510	430	
768/41	430	35	
821/41	460	335	
34/42	465	400	
117/42	440	450	
691/43	580	400	
635/44	740	445	
329/45	460	335	
1005/45	340	295	

in the volume of the heart in connection with the operation. Table 2 shows the heart volume in relation to m² of body surface, according to Liljestrand, Lysholm, Nylin and Zachrisson (1939), before and after the surgical intervention.

Fig. 2 presents radiograms before and after the operation of girl a of seven years of age.

12 out of 14 children, whose heart volume had been measured before and after operation revealed a decrease which equalled a maximum of 335 cm³ per square meter of body surface. It is evident that the extra work which involved an enlargement of the left ventricle after the ligation of the ductus has ceased. No more conspicuous changes of the general configuration of the heart were ascertainable.

During the last year, a new method has been presented at The Crown-princess Lovisa's Children's Hospital, called the hypoxia tolerance test. The patients are allowed to inhale a mixture of nitrogen and air containing 9 per cent of oxygen for 10 minutes.

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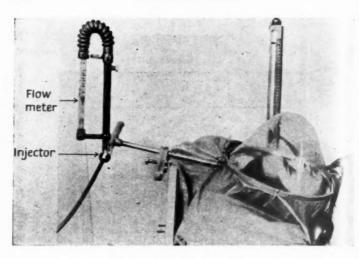


Fig. 3. Hypoxia tolerance test.

The cardiac response to this tolerance test is registered by means of electrocardiography and phonocardiography. The following has been derived from the preliminary results published earlier (Mannheimer 1946).

A normal material of thirty children showed no variations in the electrocardiogram or in the phonocardiogram during the tolerance test, in contrast to cases of rheumatic carditis, congenital diseases, and a group of cases of myocardial damage with gallop rhythm which obtained positive results from the test in a large percentage consisting mainly of variations in the S-T segments in the electrocardiogram. For this reason, there is, in my opinion, justification for the contention that the hypoxia tolerance test offers possibilities of ascertaining a cardiac insufficiency in children in quite a few cases.

Fig. 4 shows the electrocardiogram of a girl of three years of age, with patent ductus before and during the hypoxia tolerance test, with 9 per cent oxygen for 10 minutes (ECG no. 1340/45).

The hypoxia tolerance test has been applied before operation in but a few cases, since the method has not been previously avail-

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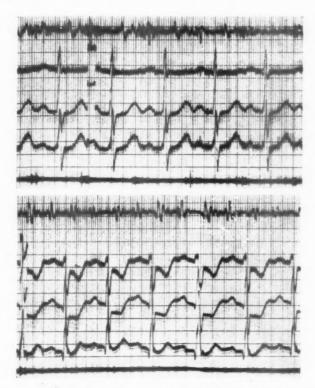


Fig. 4. Electrocardiogram from a girl 3 years (1340/45). Diagnosis: Patent ductus arteriosus, Hypoxia tolerance test. 1. Before the test. 2.9% $\rm O_2$ 10 min.

able. 12 children were examined in this way, 8 of which reacted positively. The after-examined ones have reacted quite differently.

On account of the fact that a cardiac insufficiency cannot be expected to have time to disappear until some time after the operation, only examinations performed at least one year after the intervention have been studied. Among twenty-five of these patients, two reacted positively and twenty-three negatively. 67 per cent, accordingly, had a positive reaction before the operation and 8 per cent afterwards. Thus, it is evident that the patent ductus

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cases, as a rule, have a positive test before the operation and, as often, a negative reaction after it. From this it must be concluded that their latent or manifest insufficiency disappears thanks to the surgical intervention, and that the function of the heart is normalized. This result, in my opinion, appears to be a reason more significant than most for the justification of the mode of procedure adopted at our clinic, viz., all these cases are subjected to surgical treatment.

Summary.

It is nowadays possible to make a diagnosis of patent ductus arteriosus by means of the continuous murmur and its punctum maximum over the pulmonary orifice this symptom being registrable in the phonocardiogram. It may, for various reasons be regarded as an established fact that these cases have a varying degree of latent insufficiency. This, together with certain social indications, has lead to proposed surgery in all cases of isolated patent ductus arteriosus. In Sweden, Crafoord has up till now operated on about seventy-five cases. The following results are obtained from an after-examination of thirty-three of the forty cases included in the material from The Crown-princess Lovisa's Children's Hospital. The surgical mortality rate equals one death. No recidivism occurred. All the objective and subjective symptoms of cardiac decompensation, consisting of slight cyanosis, dyspnoea, fatigue, etc., disappeared after operation. The patients' development is normal physically as well as mentally. No difference is ascertainable between them and their comrades with normal hearts. One case of septic endocarditis, with an observation period of only three months after operation, has, as far as is possible to judge, regained complete health.

The Röntgen radiograms disclosed a considerable decrease in the heart volume after the intervention.

As a rule, the result of the hypoxia tolerance test, with 9 per cent of oxygen for 10 minutes, was positive before and negative after the operation. This indicates a normalization of the cardiac function.

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Gallop rhythm and myocardial damage in childhood.

By

LARS-ERIK CARLGREN.

The connection between gallop rhythm and myocardial damage has been experimentally proved in rabbits. The gallop rhythm has been defined by means of calibrated phonocardiography and is found to be a valuable sign in the diagnosis of myocardial damage in children. The investigation is published as a supplement to Acta Pædiatrica, Vol. XXXIII.

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Heart Arrhythmias in Children 1.

By

BERNHARD LANDTMAN.

The present work has been carried out at the Heart Station of the Crown Princess Lovisa's Children's Hospital in Stockholm in the years 1945—46.

For the determination of sinus arrhythmia the author has used SCHLOMKA's frequency index. The examination revealed that the degree of sinus arrhythmia normally increases with age. Children with congenital heart disease and rheumatic heart affection exhibited less pronounced sinus arrhythmia than did healthy children. Thus the sinus arrhythmia is a normal phenomenon and a sign of a sound heart action.

The material comprised 5600 children examined at the Heart Station. Pathological types of arrhythmia were found in 126 cases. The children had all been examined by electrocardiography and most of them also by Mannheimer's phonocardiographic method. The distribution of the pathological types was as follows:

Type of	arrhythmia Number of case	28
	Extrasystoles 86	
	Paroxysmal tachycardia 5	
	Auricular flutter 6	
	Escaped beats 6	
	Sino-auricular block 7	
	Incomplete auriculo-ventricular block 5	
	Complete » » 9	
	Complicated arrhythmias	

 $^{^{1}}$ A complete report on this work is published in Acta Paediatrica, Vol. XXXIV, Suppl. I, 1947.

The pathological types of arrhythmia are described with reference to their etiology, clinical symptoms and prognosis.

Arrhythmias were not more frequent in premature infants than in other children.

Discussion on Papers 33-35.

LICHTENSTEIN stressed the value of modern cardiological methods of examination, such as calibrated phono-cardiography and the hypoxial test, in the investigation of heart cases.

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RÄINÄ: I believe that extra-systoles are more often met with if the film-registration extends over a longer period.

If Landtman's findings are fewer than mine, this is due to his registration periods being shorter. I should be interested to know their duration. My films continued for several minutes.

LANDTMAN: About 30 sec.

MANNHEIMER: I feel prompted to make the following remarks in connection with Dr. Räihä's assumption that the lack of arythmics in Dr. Landtman's premature data is due to the curves being too short. In the case of prematures long tracings extending over ten minutes present certain definite disadvantages. The infants cannot remain still and there is therefore a substantial risk of extraneous interference. It is probable that some of the arythmics present in Dr. Räihä's curves are extracardiac phenomena which there is no means of distinguishing with certainty from genuine cardiac phenomena with the one lead apparatus used by Dr. Räihä. Moreover, I should like to ask Dr. Räihä whether he has recorded ten-minute curves of fullterm babies. It is not impossible that phenomena of a similar nature would be observed also in such cases.

Roentgenological investigations of the small intestine in coeliac disease.

By

P. FLEMMING MØLLER, F. NØRGAARD and P. PLUM.

X-ray examination of the small intestine has been carried out in the Department of Pediatrics of the Rigshospital Copenhagen, since 1942. Altogether 275 children were examined, 63 of whom were suffering from coeliac disease, while 167 children had some other form of digestion disturbance and 26 were normal children. Most often each child was examined several times (up to 8 times). The total number of roentgenograms exceeded 2100.

In coeliac disease the roentgenological findings showed an abnormal motor function of the small intestine. The most prominent feature was an abnormal tonus of the bowel, segments with hypotonia alternating with hypertonic segments. These abnormal conditions were of long duration, often being present for many months after the clinical improvement. They were also found in some cases of dwarfism which presented no clinical gastrointestinal symptoms (these patients were found to present a flat blood sugar curve and an abnormally low fat absorption). The roentgenological findings described were not obtained in other gastro-intestinal disturbances.

36.

Intravenous glucose-tolerance tests relating to patients suffering from celiac disease.

By

OLLI SOMERSALO.

In order to investigate whether the low oral sugar-tolerance curve in celiac disease is due to failure of absorption or to intermediate metabolic disturbances the author has performed intravenous sugar-tolerance tests in patients suffering from celiac disease. The material comprised 13 children (of which 5 were healthy) receiving 0.5 g/kg and 9 children, including 3 healthy receiving 0.15 g/kg. The mean curves in sick and healthy children run very close to each other. These tests would thus provide evidence in favour of the theory that intermediary carbohydrate metabolism is normal in celiac disease and that impaired absorption is present.

The value of these tests would seem to be depreciated, however, by other investigation findings. It is well-known that a protracted diet rich in carbohydrates produces a low oral sugartolerance curve. But according to Crawford the intravenous sugar tolerance curve is not at all or only slightly influenced by the diet. On the other hand it has been contended that the low curve in celiac disease is due to the patient having been on a carbohydrate diet causing the carbohydrate metabolism to be stimulated to such a degree that the disappearance of sugar from the blood is accelerated beyond the normal rate. In my view it does not seem impossible that such a metabolic stimulus is not indicated by the intravenous sugar-tolerance test. Thus the authors opinion is that the problem in question is still unknown.

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Resorption research on Celiac Disease.

By ALF ØDEGÅRD.

Celiac Disease thrives in wartime. One has experienced this during the last war and also during the present. Reports both from England and Finland bear out this statement, and also in Norway the number of cases has increased. Thus, in Rikshospitalet Childrens department there were in 1934—39 in all 12 patients with this diagnosis. In the same space of time 1940—1945 there were 2½ times as many, in all 32 patients. This increasing tendency has also continued in this last year after the peace, as we mostly have 5—6—7 patients in the departement, against only on occasional one before.

I have gone through journals and partly examined 27 of these patients, and have found certain characteristics of the disease, which I will describe.

In all our cases the disease started early, earlier than is usual. On a graph one gets a natural curve which shows that the disease usually starts at the age of 8—12 month. (Fig. 1) I mean that the celiac disease is a disease wich most often starts at the age of infancy; most cases start between 6—14 mth. Only in exceptional cases does the disease start later than in the 18th month. The preliminary symptoms are often uncharacteristic. They can start by being fairly acute, but will then continue througout weeks and months as an uncharacteristic dyspepsia, with irregular bowels, sometimes soft, sometimes thicker in consistence badly smelling, and partly voluminous, sometimes vomiting. There is an early constant anorexia, without increase in weight, or even loss of weight, and the patients get bad tempered. As time goes on, after

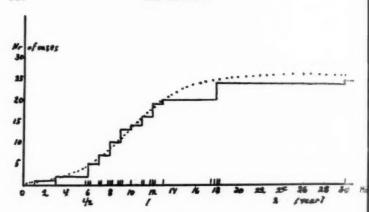


Fig. 1.

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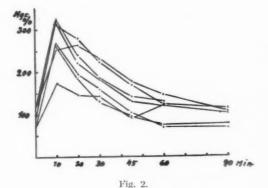
months and years, a dystrophia with thin atonic extremities develops, with fullblown abdomen, decrease in growth as we see it in the typical Celiac Disease at the age of 2—4 years.

A symptom which often occurred in our patients was pathological urine, as 18 of our 27 patients at some time during the disease showed slight amount of protein in the urine, and light pyuria. This was usually seen when the patient was at his poorest, and they were always of a passing nature. Hematurea was also seen. When microscopically examined, the urine only showed some leucocytes, otherwise nothing. The function of the kidneys was normal, and there were no urearetentions.

Tests with haemoglobin showed nearly constantly a slight anemia, during one of the phases of the disease. There was seldom less than 65 % hemoglobin. The colour index was always under 1, and hypercromic anemia, which several times has been found, was not discovered in our cases. Our patients were, however, all of them small children, mostly under 3 years of age.

The serumiron value varied between 19 and 71 gamma %, with the average at 43 gamma %, that is, on the lowest border of the normal. It seems, therefore, as if serumiron is decreased during celiac disease.

Calcium and Phosphorus in the serum often showed inflated



values. In 7 cases they were pathologically low, and in 4 of this cases there was definite tetany. Rachitis was seen in 4 cases, and scorbut in one.

Two of our patients had edemas of a passing nature in our hospital. Tests with serumprotein where made, and showed inflated values, respectively 4.1 and 5.12 mg %. Especially the fraction of the albumin was low. (2.7 and 1.9 mg %). 8 serumproteintests on other patients without edemas showed an overage of 5.8 mg %. There seems therefore to bee a tendency to low serum protein concentration in celiac disease.

This low amount of serumprotein could be brought about by the production of serumprotein in the liver not being normal, or it may be because the patient is in exceptionally great need of serumprotein during certain phases of the disease. Our two patients with edemas were both on their way to recovery.

The amount of protrombin was regularly controlled in our patients, and 4 of them were found to have a decreased amount. There was no tendency to bleeding in these patients. Probably celiac disease is the result of decreased resorbtion of minerals, vitamins and food from the intestine.

HESS THAYSEN means that an abnormal regulation of the carbohydrate is present, and that this is the reason of the low blood sugar curve which one sees through resorption tests.

MILDRED Andersen found that intravenously administered glucose disappeared from the blood more rapidly than normal. The result of this was not a slows, but a schorts curve. We in our departement find a quite normal curve when we have administered glucose intravenously in cases of celiac disease. (Fig. 2) We can therefore not find any proofs for Hess Thaysens theory. It seems as if the pathogenesis in celiac disease is explained most satisfactorily by a decreased resorption through the intestines.

Our 27 patients have been given glucose tolerance test 49 times. We find great variations of the curves. Some are low, some are steeper. The curves vary greatly for the same patients, and are not dependent on the severity of the disease. Hess Thaysen defines a curve as being low when it does not rise more than 40 % of fasting value. I found that 50 % of our curves showed just as large or a greater rate of increase. Hess Thaysen himself has pointed this out before, as he says that there only is a tendency to low curves in celiac disease. But later authors like to make the low curves a compulsory symptom. There is therefore reason to point out that the bloodsugarcurve after ingestion of glucose may vary. It may be low, and usually it is lower than normal, but it can also rise high up, just like a normal curve.

Fig. no 3 b shows in celiac disease after ingestion with glucose [2 g/kg bodyweight] an average rise of 30 mg %. Normally, (after E. Svendsgaard) a rise of 66 mg % abow fasting value is to be found Fig. 3 a. There is, as shown by the figure a great variation of the curves, and they cover each other partially. They show, moreover, that rise during celiac disease seldom exceeds 60 mg %, while, on the other hand, the rise normally is more than 30 mg %.

Even if the number of the patients is rather limited, one could be permitted to draw the conclusion that curves which show a rise lower than 30 mg % abow fasting value, probably are pathological, and could show the presense of celiac disease, while curves which rise abow 60 mg % probably are normal and seem to indicate no celiac disease. Curves which rise between 30 and 60 mg % may either be pathological or normal. In that case one must administer more glucosetolerancetests, and calculate the average.

In order to show clearly the tendency to low curves, we have



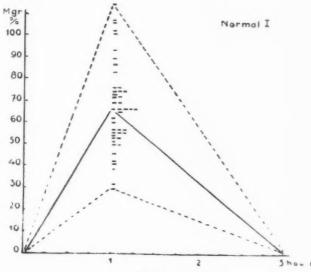


Fig. 3 a.

Above fasting value

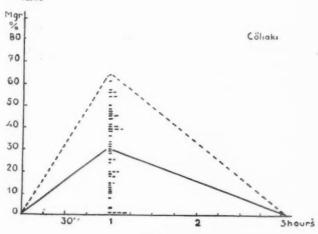
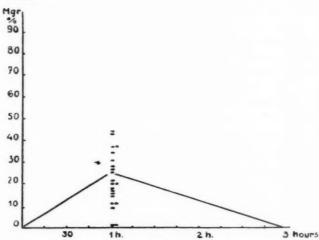


Fig. 3 b.





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Fig. 4.

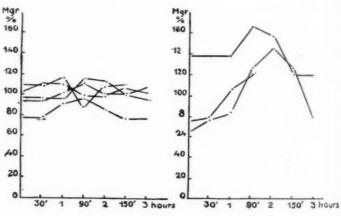
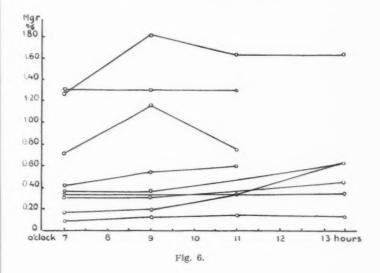
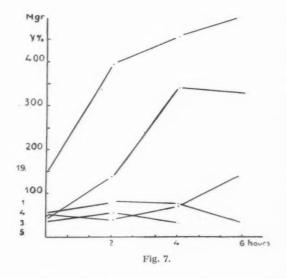


Fig. 5.





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in the childrens departement at Rikshospitalet made some tolerance tests with saccharose. We find that the average rise is somewhat smaller in tests made with saccharose than with glucose, with an average rise of 25 mg % against 30 mg %. This difference is neglectable. In normal cases the rise is also smaller in tests made with saccharose. (Fig. 4) Saccharose cannot therefore be said to be a better material for tests, in the diagnosis of celiac disease.

Some authors think that fructose is assimilated more easily in celiac disease than the other carbohydrates. We have thereformade some tolerance tests with fructose. In some cases the curve are distinctly low, and it seems therefore as if fructose is not resorbed any more easily than the other carbohydrates. (Fig. 5)

In celiac disease there is a tendency to low amounts of ascorbic acid in the serum. We have therefore made some tolerance tests with 7 mg ascorbic acid to each kg bodyweight. Normally one sees, acording to dr. Erling Rustung, a rise of 0.70 mg %. In our cases we saw a rise of only 0.24 mg %. That is 1/3 of the normal. This could therefore point to a decreased resorbtion. (Fig. 6)

To examine the resorbtion of iron, we have given ferrum reductum 0.6 g on empty stomach in the morning, and examined the increase of iron in the serum during the following hours. The increase was varied, in some cases small, or non non-existent, while in a few other cases an abnormally high rise of 350 gamma % was observed, against 1—200 gamma % in normal cases. This rise may possibly be the result of a lack of iron in the organism when the test was made. (Fig. 7)

Celiac disease is probably a syndroma which has various reasons. It may be the result of poor digestion, or partly blocked passage through the intestine wall, or through the mesenteric lymphatic vessels. The causes may therefore be various, as the disease may have its origin in these different organs.

The last few years the so called pancreatic fibrosis has been brought to our notice. This disease can develop into the typical celiac disease. It is the result of pathological pancreas and is therefore a disease wich can be separated from celiac disease syndrom.

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Intravenous glucose tests in cases of mongoloidism.

By

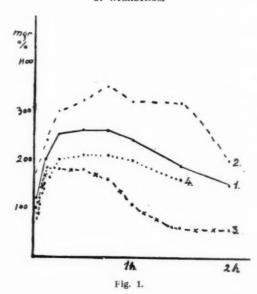
J. WICKSTRÖM.

In order to investigate a detail in the metabolism of carbohydrates in infants I have investigated the blood sugar curve after intravenous glucose injection. One would à priori expect a curve rising immediately after the injection to a maximum value and then dropping comparatively rapidly towards the fasting blood sugar value. I found, however, in several cases a curve of another type among infants showing marked mongoloid symptoms.

The glucose was injected as a 50 per cent solution intravenously in the sagittal sinus or in the cubital vein. The quantity of the injected glucose varied between 0.2 and 5.0 grammes equalling 0.1—1.0 g/kg body-weight. The injections were made slowly during the course of about 2 minutes and the position of the needle in the vein was controlled through repeated suction of blood. No technical mishap was established in these cases.

In four cases (nr, 1—4) the blood sugar curve ran as by a peroral test rising slowly to a maximum 15 to 45 minutes after the injection; in three cases it had not yet reached the fasting blood sugar value after $1\frac{1}{2}$ to 2 hours when the tests were interrupted (fig. 1).

Five cases represent another type in which the blood sugar curve immediately rose to a maximum, yet, on the other hand, dropping remarkably slowly. In one case (nr. 5 mongoloid idiot with congenital heart disease) the initial pointed top of the curve



was followed later by a slow rise (fig. 2). In cases 6—9 the curve slowly drops from its maximum value (fig. 3).

The sparse casuistics, which are of interest in these cases, appear from table 1. It should be stressed that the clinical examination showed a congenital heart disease in one case only (nr. 5).

As it is difficult to compare these blood sugar curves with each other I have yielded to the temptation of estimating an index indicating in per cent to what extent the blood sugar curve would fill a rectangle, the height of which is formed by the height of the blood sugar curve from the initial value to the highest top of the curve, the width being the time-unit 1 hour. The calculations are founded on the hypothesis that the curve runs linearly between the blood sugar values in the test series. This index retains its value in ordinary cases, i.e. in which the blood sugar rapidly returns to normal values, between 25 and 45, in the cases 1 to 4 it lies between 80 and 90 and in other cases with divergences in the course of the test curve, over 55.

How are these curious curves to be understood? It is reasonable to suppose that the injection has not been given intravenously but that the glucose solution has found its way extravasally into the

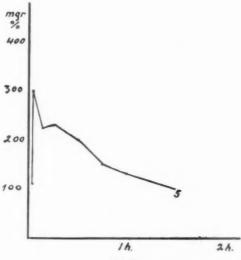


Fig. 2.

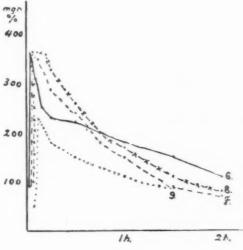


Fig. 3

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Table 1.

ŀ	do. per kg oody weight	1.0	1.0	0.15	0.5	0.4	8.0	1.0	1.0	0.35	1.9	0.5	1.0	
	njected quan- ty of glucose	2.0	2.0	1.0	5.0	5.0	5.0	4.6	4.5	2.5	2.0	6.0	2.0	
	Index	87	83	84	87	55	57	56	65	64	43	36	62	
	2 hrs	45		09			10	74	74		120	110	06	
	1½ hr	85		09	161	94	1411	88	113	90	25	120 110	125	
%	1 hr	101	315	110	192	130	82	(49		117	130	120	2101	_
But	45 min.	- 60	50 3	601				187 149	991	1261		150	245	-
in	30 min.	255 260 260 240 185 145	300 320 350 315	180 160 110	205 208	228 198 144	353 306 247 228 217 198	2411	101 356 353 353 334 260 199 172	441	260 200 145	65 1	285 260 245	_
sugar	15 min.	55 2	00 3	180	196	28	28	310 291 241	34	175 144	600	240 165	700	-
l su	10 min.		<u>m</u>	-		- EVI	472	102	553	_	21	2/	2/1	_
Blood	5 min.	- 00	240	08	63	22	062		533	13	40	10	10	
-	After 2 min.	202	21	101	501	90 2	53	363 354	563	236 213	253	103	803	-
	Before	201	160	65 110 180	97 150 163	106 290 222	853	83	0113	462	90 425 340	110 410 310	403	_
		2750 120 120 200	21001	6750		12500 1	5840	4600	4650 1	6700	2120	1720 1	2200 140 380 310	
	Weight	27	21	67	10500	125	58	46	46	67	21	17	22	
	Age	2/52	4/52	10/12	17/12	25/12	7/12	4/12	4/12	8/12	7/52	6/52	5/52	
	Diagnosis	Idiotia mongoloidea. Sten. duodeni. Sepsis.	Idiotia mongoloidea. Praematura. Sepsis	Idiotia mongoloidea	Idiotia mongoloidea	Idiotia mongoloidea. Vitium cordis congenita	Idiotia mongoloidea	Idiotia mongoloidea. Rachitis. Infectio ac.	Idiotia mongoloidea. Pneumonia	Idiotia mongoloidea	Praematurus	Praematurus	Praematura	
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tissues from which it has gradually been resorbed. The carefulness with which the injections were made, however, guarantee that this is not the case. In two cases I had the opportunity of confirming in an obduction some days later that there was no necrotic tissue caused by the 50 per cent glucose solution near the place of the injection.

It is hardly probable that the glucose solution caused a thrombus or a contraction of the vessels temporarily obstructing the passage for the injected solution. As far as I know there is no information of the endothelium being able to resorb sugar in greater quantities. The varying distribution of the glucose between erythrocytes and plasma is of no importance as the investigation was performed on whole blood. What has become of the sugar?

In case there is no congenital heart disease the injected quantity of glucose will pass the capillary system of the lungs before reaching the peripherial capillaries of the systemic circulation where the test is made. It is reasonable to suppose that the lungs in some way take an active part in the metabolism of carbohydrates.

Literature gives little information on the part played by the lungs in the intermediary metabolic processes. I have only found that the Hungarian Szendi dealt with the fetal metabolism of carbohydrates. By means of tissue analysis he believes to have established that the fetus has an autonomic carbohydrate metabolism, the active centre of which during the fetal period gradually moves over from the decidua to the placenta and from there by way of the lungs to the liver. In the 3rd to the 6th fetal month the percentage of the glucogen of the lungs is high and at this moment the lungs may thus be an active centre for the metabolism of carbohydrates. The material of Szendi also comprises human feti and his results are therefore of a certain value in this connection.

It is possible that my test curves might be explained by the injected quantity of glucose being absorbed by the pulmonary tissue and slowly returning to the blood in the same way as the sugar given per os is subject to a metabolic process in the liver. In some cases (nr. 1—4) the total quantity of the injected glucose is bound resulting in a gradual rise of the blood sugar curve (fig. 1).





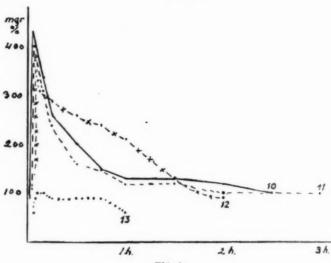


Fig. 4.

In other cases (nr. 5—9) part of the glucose passes immediately through the lungs (in case 5, the mongoloid idiot with congenital heart disease, probably a part passes directly from the right half of the heart into the major circulation) appearing in the test curve as an initial rise. The slow falling would in these cases be due to a diffusion of that part of the blood sugar which was primarily absorbed and bound in the lungs.

According to this opinion the pulmonary tissue would at least partially have retained a function from the fetal period. During infancy the mongoloid idiot would in this respect frequently remain in the fetal stage. In several cases of mongoloidism at the age of 7 to 10 years I have, however, obtained normal test curves indicating that the development stated by SZENDI for the fetus, apparently does not take place in mongoloids until the first year of life.

It is reasonable to suppose that the same phenomenon would occur in prematures. I have tried to ascertain this hypothesis by means of sugar tests on four prematures (case 10—13) at the age of 5 to 7 weeks, weighing between 1720 and 2200 grammes (Fig. 4).

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In one case (nr. 13) the injected quantity of blood sugar was only 0.2 grammes and the test curve consequently low; it rose immediately remaining high for a long time. Case 12 showed a curve with a slow descent. In the two other cases the test curve was normal. Because the procedure is dangerous the premature material is small and does not allow the drawing of any conclusions. Yet it supports sooner than overthrowns my hypothesis that the carbohydrate metabolism of the prematures like that of the mongeloids may in some cases remain in a fetal stage.

I have not had the possibility of dealing more closely with the problem to which I here wanted to call attention, but have had to content myself with vague ideas about a rare occurrence. Maybe modern technique of examination with the use of marked isotopes and possibly other methods could throw light upon the problem.

Summary.

Intravenous glucose tests with mongoloid idiots speak in favour of the opinion that carbohydrate metabolism in these (and probably also in the prematures) is being regulated in a different way than in normal individuals.

References.

SZENDI, B.: Monatschr. f. Kinderhlk. 66: 128, 1936.

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A case of concurrent vomiting in a child with electrical cerebral dysrythmia.

By

LARS GRAM.

Recurrent vomiting in a puzzling disease and clinicians who have worked with the problem have divergent opinions of the patogenesis. There are on the whole two main explanations, either that the disease is due to a lability of the intermediate metabolism, or to a nervous disposition. Many circumstances support the idea that both these mechanisms play a part, in some patients the metabolic lability dominates the picture, in others the nervous factors are most obvious. In a larger group of patients with recurrent vomiting one finds representatives for both these types. [Ström (9)].

For support of the theory of a nervous origin it has been asserted, and no doubt rightly, that the patients often are nevropathic individuals [Comby (2) Nelson (12) Schloss (6) and others]. Other investigators maintain that the disease lies more peripherally in the nervous system, in the sympathetic ganglions or in the wall of the stomach itself [Snow (8)]. Curschmann (3) and Smith (7) maintains that the disease might be an abdominal equivalent of migraine. A purely local-anatomical explanation has also been advanced, namely that the disease should be caused by gastroenteroptosis [Sherman and Koenig (10)], or intermittent duodenalstenosis [Camera (1)].

It is well known that vomiting can occur in both organic and functional brain diseases (meningitis, tumor cerebri and vomitus nervosus). These vomitings however do not resemble the clinical picture which is characteristic for recurrent vomiting in children. If it were possible to find an objective sign of changes in the brain function in these patients with recurrent vomiting, one would be a step nearer the explanation of the cause of recurrent vomiting.

In the Childrens Ward of the State Hospital we have treated a patient with recurrent vomiting, where electroenchephalography have shown sign of cerebral overirritability. The symptoms of the patient, recurrent attacs of vomiting, lasting for days, are exactly like those of patients with acetonemic vomiting, but in contrast to the findings in those patients the acetonemia was very little pronounced in our case. Acetonemia did not preceed the vomiting and did not reach a greater degree than might be expected with that degree of inanition.

The patient is a girl aged 8. From the age of two years she has had frequent periods with numerous vomitings. Five times she has been admitted to the ward during attacks, and several times the vomiting spells have started during her stay in hospital, so we have been able to follow them from the first prodroms to the finish.

The attacks have come at intervals ranging from a few days to half a year and last from 2 to 11 days with incessant vomiting. As many as 31 vomitings a day are recorded. As a rule she is conscious during the attacks, but somewhat far away and sleepy. On one occasion she had trismus and rolled her eyes and was, as it seems unconscious for some hours, respiration was very frequent. The attack ceased after an injection of calcium.

A couple of days previous to the attacks she is usually psychially changed, she is taciturn, quiet and restless. Just before the attack begins she often gets spells of sneezing. The vomitings usually come on without any apparent reason, but several times we have seen them come on after evident emotional traumata. For instance, they have started shortly after the departure of fellow patients to whom she had become attached, after a reprimand etc. Once the attack came when she was put on a ketogenic diet in effort to provoke an acetoemia. Immediately she understood she should have another diet, she began to vomit and continued to do so for many days. It is noteworthy that one has not been able to detect acetone odours from the breath nor find acetone in the urine until the attacks have lasted for one or two days.

The clinical findings and metabolic investigations made under a typical attack, lasting from 1/2 to 6/2 1946 are given i short. She began to vonit at 4 o'clock in the morning. At 2 p.m. she lay apathetically with collapsed veins. There was no smell of acetone. She had 21 spells of vomiting the first day. In blood serum Rotheras and Gerhadts reactions were negative. The plasma bicarbonate was 53 vol. % Totalbases 157 millieqv./1, chlorides

95 millieqv./1.

Urea 71 mg %. The next day she had 18 spells of vomiting. The was a definite odour of acetone in the room. The blood contained 6.5 mg % acetone. The total bases had gone down to 151 milliegy./, the chlorides to 91 millieqv./1. The total protein in blood was 9.1 %. The vomiting continued with somewhat less frequency (17, 12, 3, 1 vomiting each of the following days). The 5th day she had 12 spells of vomiting, the total acetone in blood was raised to 12.3 mg %, the total protein to 10.6 %. During the first day changes appeared in the electrocardiogram caused by the dehydration. 7 hours after the vomiting had started a roentgen examination of the stomach showed retarded passage of contrast. The diuresis was scanty during the period and the urine contained protein and coma casts. The blood-sugar concentration remained normal (92-132 mg %), but she got glucose drip enema regularly. After the attack she recovered rapidly.

X-ray examination of the stomach has been performed several times during attacks and have on several occasions shown dilation of the stomach, delayed emptying or even complete pylorostenosis. Between attacks control examinations showed normal conditions. The intermittent retention was once localized between duodenum and jejunum. As the clinical condition resembled an intestinal obstruction she was operated. One discovered two peritoneal folds which seemed to dislocate the gut. These folds were removed, but the vomitings continued to return quite as often as before. It may be mentioned that the patient had no signs of allergia.

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Encephalograph has shown normal conditions.

Belladonna preparations, ergotamine tartrate, phenobarbiton and hydantionic acid have not been able to prevent attacks, but phenobarbiton and glycose enemas have favorable affected the single attacks.

As we thought her spells might be an epileptic equivalent, an electroencephlographic examination was made. The result was as follows: Figure 1. It was registrated a scanty alphaectivity of 7—8 Hz. frequence and amplitudes of 30-60 microvols. There was in addition quite frequent outbursts of slow frequencies, 4½ Hz. — 5 Hz. — 6 Hz. with amplitudes over 100 microvolts. During hyperventilation the slow frequencies became more prominent and the amplitudes increased to over 150 microvolts. Conclusion: Electrical cerebral dysrhythmia caracterized by slow frequencies.

These findings suggests epilepsia.

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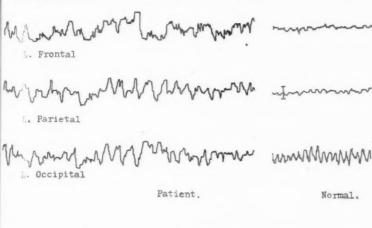


Fig. 1. Electroencephalogrem of A. H. 8 years.

It is more difficult to interprete the encephalograms of children than those of adults, and publications e.g. by Höncke (4) emphasize that it is difficult to judge findings from patients under 15 years. Our nevrological consultant S. Refsum M.D., maintains however, that the findings in this case are beyond doubt pathological, and that they give evidence of an electrical cerebral dysrhythmia such as is seen only in epilepsy: Our patient however has not had any attack which can be called epileptic. The attack of trismus and unconsciousnes which she had once during a period of vomiting could very well be accounted for by the metabolic changes caused by the vomiting.

It is not unlikely that her recurrent attacks of vomiting can be regarded as epileptic equivalents. In his survey of epilepsy Kennier Wilson (12) states that the attacks ca be of almost every kind, and that they may be visceral, as for example, vomiting. Prodromes with changes of mood are characteristic. The only thing that does not suit the the case is that the vomiting continues for days, but the explanation for this may be that only the aura and the first vomiting is of epileptic origin, and that the continuation

of symptoms depends on her nevrolability and the acquisition of the habit to vomit.

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That the electroencephalographic changes in the patient should be caused by genuine epilepsy with infrequent attacks of the ordinary type is possible, but not probable.

The recurrent vomiting in our patient are quite certainly due to a nervous disturbance with registrable changes in the brain function, but when the attack has begun, the stomach symptoms predominate. One finds namely dilatation of the stomach and delayed emptying in the course of a very short time. Her condition may perhaps be characterized as periodically recurrent vegitative crises of the stomach. As stated above, there is a striking similarity between the symptoms of this patient and patients with recurrent (acetonemic) vomiting. The local mechanism of the stomach during the attacks of vomitings is probably the same, in any case the roentgenological findings resemble those one finds with acetonemic vomiting. I our case however, acetonemia plays no primary role.

The case is presented because it shows that a cerebral overirritability can give rise to recurrent vomiting without any primary typical metabolic changes having been found. It is possible that similar conditions are evident in acetonemic vomiting where in like manner one must take into account a nervous factor.

We have not yet had the opportunity of investigating more cases of recurrent vomiting, but our findings urge that an electro-encephalography be made on these patients.

Summary.

It is given an account of a case of recurrent vomiting in a girl of 8 years. She have had her symptoms from the age of 2 years with frequent attacks of vomiting lasting several days. Her symptoms resembled closely the findings in cases of acetonemic vomiting except that the degree of acetonemia was very low and came on after the vomiting had begun. During the attacks there was a complete retention in the stomach, but when the vomitings had ceased the roentgenological findings where normal. Electroence-

phalography showed an electrical cerbral dysrhythmia and the condition of the patient was explained as beeing a visceral epileptic equivalent. As the recurrent vomiting of the patient showed close relationship to acetonemic vomiting it is argued that one ought to make an electroencephalography in similar cases.

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Discussion on Paper 36-39.

Prof. Plum: I should like to call attention to the influence of ventricle evacuation on the oral sugar-tolerance curve. I found in 1943 that duodenal administration of Glucose by means af a probe gave a normal curve in patients suffering from celiac disease, whereas the curve for sugar taken per os was flat. Somewhat earlier, MAY and McCreary had published identical results. Further, I wish to include the motorial function of the small intestine in the discussion on athrology. We know that absorption is dependent physiologically on the motion of the small intestine, and since the motility of this organ is not normal in celiac disease, as is shown by the roentgenological findings demonstrated in my communication, one might reasonably assume that the cause of the poor absorption present in this complaint is to be found in the abnormal motorial function.

C. FRIDERICHSEN: Prof. Plum's interesting roentgen demonstrations have brought special interest to bear on the reaction and resorption capacity of the small intestine. In this connection I wish to mention an article by Freise and Jahr (Jahrb. f. Kinderk. 110—205—1925), in which it is

proved by roentgenological findings that the poor benefit derived from food is due to the motility of the ventricle, the jejunum and the proximal part of colon being strongly increased. The authors therefore treated Celiac disease with opium, whereby better resorption of the food was obtained.

PALMBERG: A case of celiac disease exhibiting spontaneous glucosu [a.] In connection with the papers bearing on this subject I should | ke to show some results obtained from observation of a case of celiac disease with spontaneous glucosuria.

The girl is an inmate of a children's home, born 28. 9. 39. Since 1941 she has been admitted four times to the children's section of Åbo County

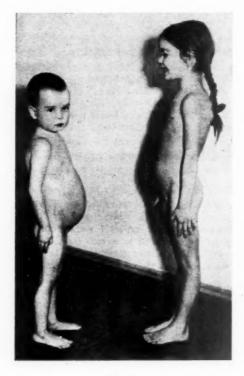
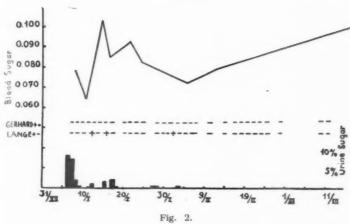


Fig. 1.

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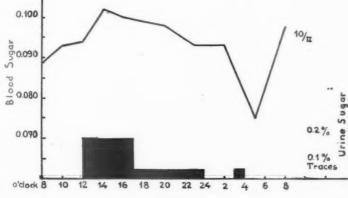
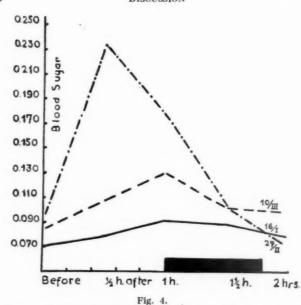


Fig. 3.

24-hour Curve for Blood and Urine Sugar at normal diet.

Hospital for treatment of a serious form of typical celiac disease. During her last stay at the hospital, from 28. 12. 45 to 19. 3. 46, she looked as in Fig. 1. The girls are of the same age. The dilated stomach and retarded physical development of the celiacia patient on the left indicate the nature of her illness. All symptoms af typical celiac disease were present.

We measured the sugar content in blood and urine and the ketone corpuscles in the urine (Fig. 2). Distinct glucosuria was recorded in the 17 - Acta pædiatrica. Vol. XXXV.



Tolerance for different kinds of Sugar administered in different ways.

initial stages of treatment, combined with slight acetonemia. The excretion of glucose in the urine ceased when her general condition and the working of the bowel improved, although the fasting blood sugar values remained practically unaltered.

From the blood- and urine sugar curve extending over 24 hours (Fig. 3) we see, however, that the glucose seeps through when the blood sugar attains its highest values during the second half of the 24 hours.

Glucose tolerance tests (Fig. 4) show that the blood sugar curve is very flat. The fructose curve has somewhat higher values, whereas glucose i.v. produced considerable glucemia, although half a dose only was used. Sugar was detected in the urine only when added i.v. The tolerance tests were always based on fasting values.

The results of the investigation speak in favour of the theory that celiacia disturbs the phosphorylation process. The glucose is absorbed with difficulty through the walls of the intestine and can pass through

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only after having been phosphorylized. Fructose is absorbed with greater ease and need not be phosphorylized. If intestinal absorption is eliminated and glucose is injected intravenously, the blood sugar values promptly rise.

In a system which functions normally the glucose seeps through glomenuli and is thereupon entirely absorbed in tubuli. If the assumption that a general impairment of the phosphorylation process is present in celiacia be correct, it would follow that the absorption process within the tubuli would also be inadequate. My case supports this theory. We observe that when the general condition is poor and the intestine functions feebly, tubuli fail to perform the additional work required if the filtration of glucose through glomenuli is in the least increased by a normal (Fig. 3) or an induced (Fig. 4) increase of blood sugar. Otherwise the dilution and concentration faculty of the kidneys, when tested with Volhardt's water test, proved to be good. In the literature I have not seen glucosuria mentioned in connection with celiacia. It would seem that this line of investigation has not so far been followed. At present there is again a case of celiacia with spontanous glucosuria in our hospital, but the observations relating to this case are not yet complete.

J. Ström: This case of electric cerebral dysrhythmia observed in a child suffering from severe attacks of vomiting seems to me to be very interesting. However, I was struck by the circumstance, which was also emphasized in the paper, that the patient did not show any symptoms of acetonuria at the beginning of the attacks and that the ketonemia was very slight while they were in progress. The diagnosis, recurrent vomiting associated with ketonemia, would seem to require the presence of both components of the picture, viz vegetative irritability and metabolic disturbances.

The case reminds me of a young woman whom I was twice called on to examine in an advisory capacity in the department for internal disease. She had had several spells of very severe vomiting and had on two occasions been operated on for ileus. It was suspected that her attacks were of the same type as recurrent vomiting with ketonemia in children. However, in her case there was never any acetonuria at the onset of the attacks. The patient was of a pronounced hysteroid type and it was evident that the spells were brought on by psychic factors. As known, no cases of the illness occurring after the years of puberty have been described. In this case I drew the conclusion that the cause was of a purely psychic nature. The possibility of the case being an equivalent of epilepsy was also advanced.

Further observation of the electroencephalography in cases of recurrent vomiting in children would seem to be of great interest.

Studies on Diphteria.

By

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The incidence of diphtheria in Sweden has for many years been low, considerably lower than in several neighbouring countries. In 1942 an upward trend set in, probably due to the influx of refugees, but now the rate appears to be declining once more.

As a result of the long period of low morbidity, the natural resistance to diphtheria is exceedingly limited, to the extent that not more than about ten percent of the adult population of Sweden are now immune (negative Schick reaction or diphtheria antitoxin titer of ≥ 0.02 antitoxin unit per cm³ of serum).

This state of affairs is most unfavorable from the standpoint of epidemiology. It has, however, provided an unusual opportunity to study certain problems of immunity in connection with diphtheria.

1. Infantile immunity against diphtheria. Immunization of infants by various methods.

Since only a small percentage of the adult population of Sweden is now immune to diphtheria, mothers are seldom able to confer on their offspring the passive immunity previously reported to be the rule during the first six months of life. Therefore the question of immunization arises even at this early age (B. Vahlquist and N. G. Persson, Svenska Läkartidningen 1945, p.). There are two methods of dealing with this problem: a) immunization of

Table 1.

, Group	No. of	antitox	persons with titer (exper cm³ of	pressed	Maximum value	Median value	
	Cusco	< 0.0005	$\ge 0.0005 \ < 0.02$	≥ 0.02	-		
1	15	Ó	0	15	<2.0 >1.0	0.30	
2	14	1	2	11	<1.6 > 0.8	0.075	
3	16	2	5	9	=2.0	0.075	
4	12	4	2	6	< 1.10 > 0.05	0.015	
5	15	5	6	4	< 0.20 > 0.10	0.0015	
6	38	30	7	1	< 0.05 > 0.02	< 0.0005	

the mother during pregnancy with diaplacental immunization of the child as a result, or b) direct immunization of the child.

- a) Immunization via the mother. 27 women were immunized during the last few months of pregnancy. In 18 the newborn infant showed ≥ 0.02 unit of diphtheria antitoxin per cubic centimeter of serum, with a maximal value of < 14 > 12.5 units. In only a small number of cases was the titer still high enough after the first three months of life to indicate immunity.
- b) Direct immunization of infants. The series consisted of three groups of about 15 infants each, divided on the basis of age, namely: newborn, 2 to 3 months, and 6 to 8 months. Even the newborn were found to react with the formation of antitoxin (highest level recorded: <0.20>0.10 unit per cm³ of serum), although at a slower rate than older subjects. From the age of two months, however, the immunization effect corresponded to that in older persons.
- 2. The duration of immunity following immunization against diphteria compared to that after passing through the disease or the carrier state.

The investigation was conducted on five different groups of individuals. The results are summarized in Table 1. Also included in the Table is a control group consisting of individuals who were not immunized to diphtheria and who, as far as could be discovered, had never had the disease.

Group 1: Immunized to diphtheria (two injections of vaccine, one of 1.0 cm³ and the other of 0.5 cm³ with an interval of one year; determination of diphteria antitoxin titer one year after the last injection).

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Group 2: Former carriers (about two years previously).

Group 3: Former clinical diphtheria patients (about two years previously).

Group 4: Former carriers (about 20 years previously).

Group 5: Former clinical diphtheria patients (about 20 years previously).

Group 6: Control group.

It appears from the Table that the most satisfactory resistance is exhibited by Group 1, in which active immunization was done. The maximum values of Group 2 and 3, comprising subjects with carrier state or clinical diphteria about two years earlier, were the same as those of Group 1, but low titers in several cases depressed the median value below that of Group 1. Of the two remaining groups in which the disease or the carrier state had occurred 20 years previously, one third showed no antitoxin titer, i.e. < 0.0005 unit per cm³ of serum. In addition, the median values were considerably lower than in the first three groups. The state of immunity of the former carriers appears to be somewhat better than that of the former clinical cases.

The starting point of the present investigations was the low incidence of diphtheria that has long prevailed in Sweden. Nothing definite is known of the causes of the low morbidity of this disease. It may be that an antibiosis between certain of the micro-organisms normally present in the throat, on the one hand, and the diphtheria bacilli, on the other hand, is a contributing factor. This possibility will be explored in later investigations.

For detailed figures, discussion of the results and references the reader is referred to papers shortly to be published in Acta Padiatrica.

Discussion on Paper 40.

KJellberg: Between August 1945 and June 1946 about five thousand foreign children arriving in Sweden were examined during their stay in quarantine to ascertain the number of carriers of diphtheria bacilli (culture according to Clauberg). The investigations gave the following results (approximate figures):

		Number	Percentage of	carriers of
			bacilli	
Norwegian	children	2000	0.1	
Dutch		1900	18.0	
French	9	800	12.0	

After personal contact had been established between Swedish medical officers and the medical authorities of the respective countries for more effective diphtheria control prior to the children leaving for Sweden: (in Holland culture according to Clanberg or similar which was not the case in France).

Dutch	children	about	500	0	%		
French			400	4	%	(preliminary	figure)
9			600	9	%		

Doc. Wickström: Demonstrated curves showing the incidence of diphtheria in Finland. In spite of a morbidity of about 100 cases per 100,000 inhabitants during the years 1934—1942, an epidemic broke out in 1943 which carried off about 3000 patients during 1943—1945, the morbidity rate being 370, 407 and 488 per 100,000 inhabitants for each year. Prophylactic vaccination of more than half a million individuals was carried out, mainly of children of schoolage. This age-group is no longer represented to any degree worth mentioning in the hospitals for infections diseases, whose case material chiefly consists of youths aged 15—25. Prophylactic vaccination of all children in conjunction with inoculation against small-pox is now being contemplated, two injections to be administered with an interval of one month. The vaccination should be repeated immediately before the children start on their school career and after its completion.

Rantasalo: I have adopted treatment with pyrisan to destroy the bacilli in carriers of diphtheria infection. Pyrisan is a B. faecalis-alcaligenes emulsion of finnish manufacture, which is injected intravenously. It causes fever, the degree of which is determined by the size of the doses. This method was resorted to after it had been observed that the bacilli disappeared in diphteria patients as a result of fever attacks brought on by the illness.

More than 450 courses of treatment have been carried out. At first the injections were given at intervals of a few days, which did not, however, produce satisfactory results. Later 1—2 injections a day were administered, the best results being then obtained by 5—7 injections. According to SAARELMA's report, 84 per cent were freed from bacilli during the observation period extending to two weeks, whereas the corresponding figure in the control group, comprising 1412 cases, was 45 per cent.

In the whole material the result is better the later the treatment is started: in the 1st to 3rd weeks 54 per cent, in the 4th week 69 per cent, in the 5th 74 per cent and in the 6th—16th weeks 78 per cent.

The best results are obtained in throat diphtheria, the poorest in nose diphtheria and in carriers of bacilli. Of the patients over 20 years of age 86 per cent were freed from bacilli, and 71 per cent of the patients below that age.

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41.

Clinical-experimental Investigations on the Absorbtion of Ascorbic Acid with simultaneous Administration of Cod-Liver Oil or Concentrations of A- or D-Vitamine.

By

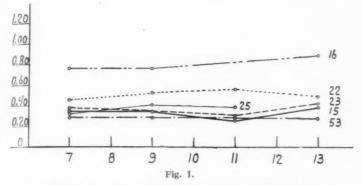
E. RUSTUNG.

The object of the investigations has been to endeavour to throw light upon the practically important question whether there exists an antagonistic relation between cod-liver oil, or A- or Dvitamine, on the one hand, and ascorbic acid on the other hand. Previous investigations which have been made partly with codliver oil and partly with its separate constituents, and chiefly by experiments on animals, have not shown concordant results. The findings in my own investigations will bee seen from the table and the figures. In these experiments it has been sought to ascertain whether an antagonism of the kind mentioned can be noted with respect to the absorbtion of ascorbic acid. From these investigations it must be permitted to conclude that with respect to the absorption of ascorbic acid no antagonism of practical importance is evinced by cod-liver oil or by the A- or D-vitamine. In these investigations it has, as stated, been sought to elucidate the question whether as regards the absorbtion of ascorbic acid an antagonistic action is exerted by cod-liver oil or by any one of

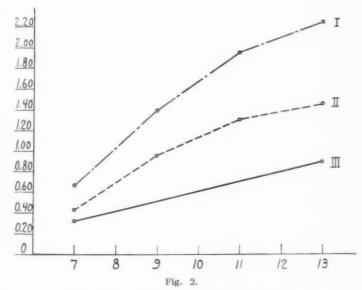
Table of the experiments and their results

(The figure in parentheses beside the mean value for serum ascorbic acid indicates the number of observations on which the mean value is based).

Nature of experiment	S mg %,	Serum ascorbic acid in mg %, at 7, 9, 11 and 13 o'clock	bic acid if and 13	n o'clock	Figure	Designa- tion in
	7	6	11	13	140	figures
No administration of ascorbic acid in any form 0.42(6)	0.42(6)	0.44(6)	0.35(5) 0.40(6)	0.40(6)	1	
2 grammes hip-powder per kg of body weight to children under 1 year old	0.32(5)			0.89(5)	2	Ш
2 grammes hip-powder per kg of body weight to children aged from 4 to 10 years	0.42(6)	0.95(6)	1.30(6)	1.45(6)	23	п
2 grammes hip-powder and 2 ml cod-liver oil per kg of body weight to children aged from 4 to 10 years	0.66(5)	1.39(5)	1.94(5)	2.24(5)	2 and 3	-
f gramme hip-powder and 3 ml cod-liver oil per kg of body weight, to one 7-year old child	0.33(1)	0.92(1)	1.58(1) 1.65(1)	1.65(1)		
About 7 mg ascorbic acid per kg of body weight to children aged from 4 to 10 years	0.66(10)	1.11(9)	1.11(9) 1.14(5) 1.18(10)	1.18(10)	4	>
About 7 mg ascorbic acid and 2 ml cod-liver oil per kg of body weight to children aged from 4 to 10 years	0.49(5)	0.78(5)	1.14(5)	1.41(5)	4	IV
About 7 mg ascorbic acid and about 9000 I.U. of vitamine A per kg of body weight to children aged from 4 to 10 years 0.47(8)	0.47(8)	1.12(8)	1.10(7)	1.10(7) 1.04(8)	4	IV
About 7 mg ascorble acid and about 25000 LU. of D-vitamine per kg of body weight to children aged from 4 to 10 years, 6.27(5)	0.27(5)	0.71(5)	0.71(5) 0.79(2) 0.75(5)	0.05(5)	4-	7.13



No administration of ascorbic acid in any form (individual curves).

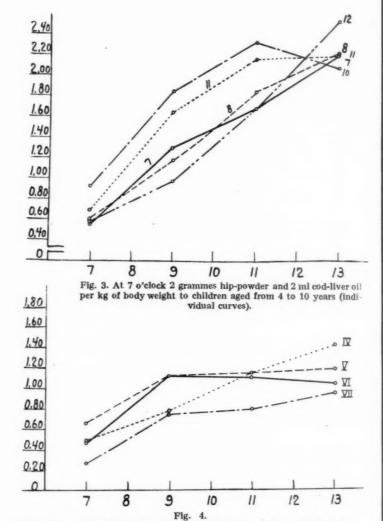


At 7 o'clock 2 grammes hip-powder and 2 ml cod-liver oil per Curve I: kg of body weight to children aged from 4 to 10 years.

Curve II: At 7 o'clock 2 grammes hip-powder per kg of body weight to children aged from 4 to 10 years.

Curve III At 7 o'clock 2 grammes hip-powder per kg of body weight to

children under 1 year old.



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Curve IV: At 7 o'clock about 7 mg ascorbic acid and 2 ml cod-liver oil per kg of body weight to children aged from 4 to 10 years.

Curve V: At 7 o'clock about 7 mg ascorbic acid per kg of body weight to children aged from 4 to 10 years.

Curve VI: At 7 o'clock about 7 mg ascorbic acid and about 9000 LU. of vitamine A per kg of body weight to children aged from 4 to 10 years.

years.

Curve VII: At 7 o'clock about 7 mg ascorbic acid and about 25000 I.U. of
D-vitamine per kg of body weight to children aged from 4 to
10 years.

its constituents. But another matter, which has not here been taken into consideration, is the question whether an antagonistic relation arises after absorbtion.

A more complete acount of these investigations will be published in norwegian in Nordisk Medisin (Forhandlinger i Det Norske Medicinske Selskab).

42.

Studies on the urinary excretion of thiamine in children.

By

ANNIE SCHONDEL.

Except in the Far East, beriberi is very seldom encountered in children. 5 cases of this disease in children have however been reported in Europe, and 24 cases in America. Here, in the Pediatric Clinic of the Rigshospital, we have seen one case of secondary beriberi in an infant with chronic dyspepsia. Previously attempts have been made to demonstrate the presence of hypovitaminosis $\mathbf{B_1}$ in children by treating their presumable symptoms of $\mathbf{B_1}$ deficiency with vitamin $\mathbf{B_1}$ preparations. Most often, however, such preparations contained also other components of the vitamin B complex, making this proof very uncertain.

The synthesis of thiamine gave rise to chemical methods that made it possible to determine fairly rapidly the B₁ content of various body fluids including the urine.

Until recently the vitamin B_1 metabolism in children has been investigated only superficially, for which reason we have taken up the question of whether hypovitaminotic conditions in children suffering from various diseases may be demonstrated by determination of the amount of vitamin B_1 excreted with the urine.

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The technique employed here has been the Jansen thiochrome method as modified by Westenbrink & Goudsmit: the thiamine is removed from the urine by adsorption with aluminium silicate; after washing, the thiamine is again separated from the adsorbent with alkali, and then oxidized to the fluorescent thiochrome. From the measurement of the fluorescence the vitamin B₁ content of the urine can be calculated.

The thiamine excretion is determined by examination of the urine over a 24-hour period and, as a rule, at least 3 tests are made in each case.

For normal material we have partly used children in good health (from a children's home) and partly children admitted to this clinic for lesions that cannot conceivably influence the vitamin B_1 metabolism.

One result of the present investigations has been that, on the whole, the Danish diet does not give rise to hypovitaminosis B_1 . But, certain diseases that are treated by diet may involve a risk of the development of this condition. This applies, among others, to hepatitis on a diet very rich in carbohydrate, epilepsy on a ketogenic diet, and to protracted dyspepsia.

The urinary excretion of thiamine was determined in 110 healthy children, from 1 month to 14 years old (24 girls and 86 boys) and ranged between 2 and 361 γ . The excretion increased with increasing age, so that the greatest increase occured in the first year, where the minimum and maximum results are 2 and 94 γ thiamine; in the next 2 years they are 61 and 118 γ . From 3—14 years the average falls between 118 and 361 γ (one girl with a very low diuresis excreted only 74 γ). On graphical presentation of the case histories of the children over 3 years we have a figure with a maximum result between 200 and 250 γ . When this case material is divided into 2 groups, 39 boys and 23 girls, a slight difference is found as the boys excrete 222 γ and the girls 198 γ thiamine.

These results correspond very well with those obtained from normal children by American and Dutch investigators. On an average, the American results are higher.

In order to investigate the influence of the diet on the urinary

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excretion of thiamine, the calories, carbohydrate and thiamine contents of the diet for normal children, are calculated. For the infants the diet was found, on an average, to contain $50\,\gamma$ thiamine per 100 cal., of which 2—23 % was excreted, with an average of 10 %, showing a slight increase in the excretion with increasing age. For 29 of the 62 older children the diet was found on an average to contain $58\,\gamma$ thiamine per 100 cal., and 15— $28\,\%$ of this was excreted, averaging 20 %. Corresponding degrees of excretion have been found in adults. The American authors claim that in normal older children the thiamine excretion should exceed 20 % of the thiamine ingested. Also the absolute excretion found by these authors was considerably higher than observed in this material. The urinary thiamine excretion is distinctly dependent upon the amount of thiamine ingested: the greater the thiamine content of the diet, the greater is the thiamine excretion.

The casematerial consists of children suffering from chronic dyspepsia, coeliac disease, anorexia and hepatitis, together with patients on various particular diets such as diets for acidosis, enteritis and reducing.

27 dyspeptic infants were examined between the ages of 2 and 9 months. The diet consisted chiefly of thin, acidified, mixtures of cow's milk, while a few were also given mother's milk. As in the normal casematerial, there is a wide variation of the results obtained. For these patients the thiamine excretion varied between 2 and 69 γ but the difference from the findings in the normal cases was not significant. All the children were underweight, and the milk mixtures were thinner than usual for their respective age, but the intake of calories per kg of body weight had been normal, and the same applies to their intake of thiamine per 100 calories. On an average they excreted 12 % of the thiamine ingested, which corresponds to the excretion in the normal cases. Gradually, as the children improved and were getting stronger milk mixtures, the thiamine excretion increased.

The above-mentioned child with beriberi was a boy, 6 months old, in whom a severe degree of fat dyspepsia was after some months followed by oedema, which persisted for several months and subsided only after treatment with thiamine. His thiamine

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excretion with the urine was 18 γ , and the blood contained 4.4 γ % thiamine — that is, a subnormal content. Also his thiamine intake was too low.

Altogether 8 patients with coeliac disease were examined — 7 boys under 2 1/2 years and a girl of 13. The average excretion for these boys varies between 8 and 68 y thiamine, and that only in one instance does the result exceed the average value for the regression curve. Indeed this was the child who was least affected, and he had been treated with vitamin B complex one month before. All the other children were examined soon after the admission, while the general condition was poor. The diet had been poor in fat, rich in protein and carbohydrate. Their intake of calories per kg had been normal, but carbohydrate calories amounted to about 70-80 %, which is higher than in a normal diet. The vitamin B, intake corresponded to that in the normal cases, but, calculated per 100 carbohydrate calories, it was lower than normal. In 3 of the patients the excretion was undoubtedly too low for their age. Indeed these children were more affected than the others, and they excreted 11 % of the vitamin B1 given. Two of them were examined several months later, and then the excretion had increased to a normal level. The 13-year-old girl excreted only 74γ — considerably below the normal level. In her case, too, 80 % of the diet consisted of carbohydrates, which may very well explain the low thiamine excretion.

11 patients with anorexia were examined at the age of 3—9 years, and their thiamine excretion was between 72 and 108 γ . In 3 of these cases the excretion was undoubtedly below the normal level, while the others showed normal variations. Indeed these 3 children took less food than other children of their age, and they excreted between 11 and 15 % of the amount of thiamine ingested, which was normal per 100 calories.

Among 4 patients who were suffering from hepatitis and received a high-carbohydrate diet, the thiamine excretion was considerably below the normal in three, while in the fourth it was at the lower limit of the normal. The thiamine intake of these patients was normal, but carbohydrate made up 82 % of the total calories as against 46 % in the normal cases. This low rate 18 — Acta pædiatrica. Vol. XXXV.

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of excretion is probably attributable to the fact that thiamine $i_{\rm S}$ required for the combustion of carbohydrates.

In two epileptics, who for several months had been kept on a ketogenic diet, the thiamine excretion was likewise subnormal (26 and 51 γ , respectively), but the diet contained only 18 γ thiamine per 100 calories.

In the acute state of enteritis, when the patients were given a boiled water and apple diet, the thiamine excretion was low, but it increased very rapidly as soon as the patients were given more food. The same phenomenon was observed during fever.

In diabetics the thiamine excretion was found to be normal—from 147 to 285 γ —likewise in patients with adipositas, 81—300 γ . On reducing diet, the thiamine excretion decreased somewhat.

In addition, some tolerance tests were performed with oral administration of thiamine. This form of administration was considered better physiologically, because the tissues thus are allowed sufficient time to absorb the substance — in contrast to parenteral administration by which the organism is flooded with thiamine, so that the excretion takes place very rapidly. In these tests the surplus excretion was determined by subtraction of the spontaneous 24-hour excretion from the result obtained on the day of the test, and then it was calculated in percentage of the amount ingested.

Altogether 44 normal children were given 2 mg thiamine by mouth, and they were found on an average to excrete 16 %, with variations between 3.8 and 47 %. Most of the values obtained were over 10 %. The absorption from the intestinal canal proceeded rapidly, as 31 % of the entire 24-hour excretion was found within the 3 first hours.

Among the patients on whom the test was made, the anorexia patients excreted on an average 10.2 %, the diabetics 14 %, and adipositas patients 12.6 %, i.e., within the normal variations.

In contrast hereto, the surplus excretion was distinctly lower—being less than 4 % of the test dose—in hepatitic, epileptic and enteritic patients. In patients with coeliac disease the surplus excretion was a little lower than normal. This means that the

tolerance test gives low values in the same patients in whom the spontaneous urinary thiamine excretion is subnormal, thus confirming the latter finding.

Nearly all the low values obtained in the present casematerial may be explained as attributable to the particular composition of the diet, either very rich in carbohydrate or very poor in thiamine. In no case was there any sign of a defective absorption of thiamine, as the excretion increased rapidly as soon as thiamine was given daily.

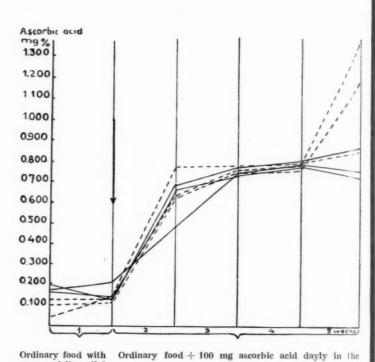
The conclusions drawn from the data here reported will then be that an extra addition of thiamine should be given to patients on a high-carbohydrate and ketogenic diet, in protracted dyspepsia and in febrile conditions. It is preferable, however, to give a vitamin B complex preparation, as usually the other vitamins B will be needed too.

Discussion on Paper 41.

Dr. Sundal: In relation to Dr. Rustung's communication I should like to demonstrate some tolerance tests which were carried out in 1942—43 on children under and up to the age of 12. Ascorbic acid was administered, partly in conjunction with cod-liver oil, partly alternately with a concentrate of cod-liver oil (A—D vitamin) administered at quite a different time of day.

24 healthy children aged from 5 months to 12 years were given doses of 100—200 mg of ascorbic acid every night. Half of the children took proportionate quantities of a mixture consisting of ascorbic acid and cod-liver oil and the other half were dosed with ascorbic acid in the morning and a concentrat of cod-liver oil at night.

The curves for ascorbic acid in the blood, which were established once a week during the test period covering 4 weeks, do not provide conclusive evidence to show that ascorbic acid administered with cod-liver oil produces different results from pure dosages of acid without admixture of cod-liver oil.



conc. cod live oil 3
times weekly at
breakfast.

with conc. cod liver oil 3 times weekly at
breakfast.

with 10 g cod lives oil mixed together with
100 mg ascorbic acid in the evening.

Fig. 1. Ascorbic acid values in blood serum of 6 children in the age between 5 and 8 months.

Nov. to Dec. 1942.

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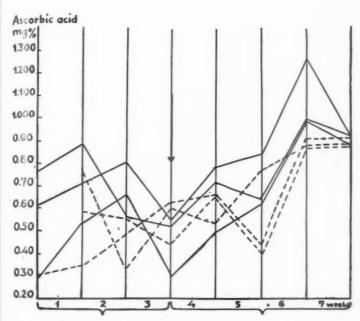
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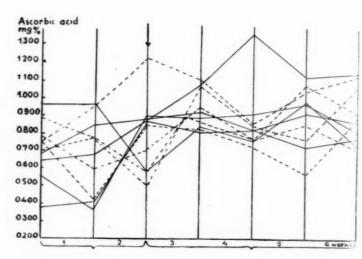
Diet: Ordinary food with concentrated cod liver oil 3 times weekly at the break fast.

Diet: Ordinary food + 100 mg ascorbic acid dayly at the evening meal.

with conc. cod liver oil 3 times weekly at the breakfast.

 with 10 g cod liver oil mixed together with ascorbic acid at the evening meal.

Fig. 2. Ascorbic acid values in blood serum of 6 healthy chldren at the age of one year.
Sept. to Oct. 1942.



Diet: Ordinary food with concentrated cod liver oil 3 times weekly at breakfast.

Diet: Ordinary food + 200 mg ascorbic acid dayly at the evening meal.

with conc. cod liver oil 3 times weekly at breakfast

with 10 g cod liver oil mixed together with 200 mg ascorbic acid at the evening meal.

Fig. 3. Ascorbic acid values in blood serum of 10 healthy school-children in the age between 8 and 12 years.

Nov. 1942 to Jan. 1943.

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The care and prevention of pes planus in the child of pre-school age.

By

PER J. NORDENFELT.

The frequency of weak and flat feet has now reached alarming proportions. The main reason why the foot loses its shape and its ability to function to the fullest degree is to be found in weakness of its muscles. The muscles are of prime importance in maintaining the posture of the foot, although the tendons, the ligaments, and certain static factors also are of significance in this respect.

Muscular weakness, in turn, depends on our unnatural mode of life which from an early age, prevents the muscles from developing harmoniously to their full power. Factors that inhibit muscular development are the one-sided strain on the feet that results from standing and walking on hard floors and roads, the generally unsatisfactory physical upbringing of children, and, last but not least, unsuitable footwear.

Constitution also plays a part in pes planus. Certain families, for example, exhibit poor muscular tone, others a tendency to obesity, possibly of endocrine origin. Both conditions make for poor posture, particularly of the feet. Rickets has always been regarded as a strong contributory cause of flat feet. It is my opinion, however, that the importance of this condition has been exaggerated and that nowadays at least it is of minor significance in this connection. After all, the frequency of rickets has decreased considerably during the past few decades, at the same time as flat feet appear to have grown increasingly common.

It may be assumed that the newborn child has a healthy foot and a good muscular build. Congenital flat feet are exceedingly gare, but when present should be submitted to early treatment.

During the first years of life all children appear to have flat feet. Investigations by Spitzy at the beginning of the century revealed that the arch at this time is filled in with fat, which does not disappear until the age of about three years. In addition, Böhm showed that infants and children have relatively lower arches than normal adults. It is a physiological phenomenon that when the child begins to walk the arch drops when the weight of the body is put on it, but regains its normal shape when the weight is removed. This weakness generally disappears at the age of three, although in many cases it remains until considerably later. Some orthopedists claim that even if pes planus in small children generally is not pathological, a valgus deformity is always abnormal. Böhm, however, considered he had proved that a purely physiological valgus position may be present in early childhood.

Foot defects in childhood seldom cause pain, but are more likely to be manifested in the form of impaired function.

The prophylactic care of the foot should begin early and be aimed primarily at the general development of the muscles and the elimination of harmful influences. Efficient prenatal and infant care, with special stress on anti-rachitic measures, is, of course, an essential part of the programme.

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The infant should be allowed to move its limbs freely from the first weeks of life. Garments that curtail movement should be avoided. For the lower part of the body a diaper fastened loosely around the waist is quite sufficient, the girdle or swaddling band, still common in some countries, being unnecessary. This type of garment restricts to a not inconsiderable degree the movements of the spine and hips. Feet and legs should be naked or possibly enclosed in a roomy bag with shoulder straps. Stockings or socks should never be used — they limit the movements of the feet and particularly of the toes. According to Thomsen, it has been calculated that a baby with bare feet flexes and stretches his toes two or three thousand times a day; socks reduce these movements considerably. When a baby is lying in bed with a coverlet



Fig. 1. Socks shaped differently to fit the right and left feet.

over him, there is slight danger of the feet becoming cold, even if they are bare. In that case, the hands, which are above the covers, would more easily be chilled, but it would never occur to even the most zealous mother to put mittens on a baby indoors.

It is important that the infant is not helped to stand before it is able to rise to its feet itself. The feet should not be burdened until they are strong enough to carry the weight of the body. Crawling is a part of the natural development, and this stage should not be omitted. Standing at too early an age strains the arch and may stretch the plantar aponeurosis, thus contributing to the development of flat feet. This applies particularly to heavy, clumsy children. Standing on a soft surface is, of course, especially unsuitable. For that reason it is advisable to avoid cribs with high sides, or at least to see to it that the child does not stand in bed for long periods. The popular play-pens, which in many cases are a necessity, also have the disadvantage that the child

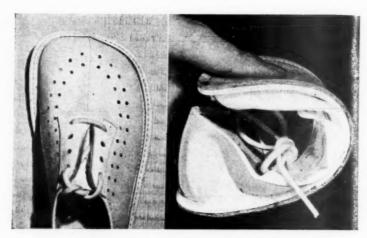


Fig. 2. Children's shoes with completely soft soles.

is able to pull itself to its feet and often stand for long periods before it is ready for this effort.

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Throughout infancy and even far into the pre-school age, it is wisest to allow the child to be barefoot as much as possible. Roomy socks, shaped to fit the feet, i.e. a right and a left sock, and later on shoes with completely unstiffened, pliable soles may be used on occasions. Barefoot is best, however. According to Thomsen, Runge and many others, the high, laced boots with rigid soles that used to be so common are entirely unsnitable, particularly when the child is learning to walk. Children's feet require no support. Nor does a boot give effective support. Instead, it prevents the child from moving its toes and feet so that the muscles can develop naturally. And it is strong muscles alone that can provide effective support.

In order to avoid faulty posture of the feet during the preschool age, the child must be given an opportunity to satisfy its great need of movement. It must not be hedged in by restrictions that prevent its moving freely about in the cramped quarters in which so many families unfortunately have to live and even from climbing on the furniture within reason. It is not natural



Fig. 3. Good type of firm shoe, although the sole is somewhat too thick and stiff.

for children in the pre-school age to walk, especially on hard roads and streets; nor do they do so voluntarily. The constant burden on the feet entailed in walking without the muscles being given free play is harmful. In cities children up to the age of at least three years should be taken in pushcarts to the playground, where they can run and jump about as much as they want to. The ideal environment for the growing child is, of course, the country, where its feet are exercised in a natural way without strain.

Pre-school children should not be bundled up in garments that restrain their movements, and they should go barefoot as much as possible. Going barefoot in the woods and fields is of the greatest value, since walking on uneven ground provides exercise for all the muscles of the body, especially those of the foot. At every step the toes spread and grip the ground in a natural manner. The value of going barefoot out of doors in warm weather in the country is generally agreed on. Opinions differ, however, as to the advisability of going without footwear indoors. Numerous orthopedists advocate this, while others, including several Scandi-

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navians, recommend firm shoes for smooth floors. In my opinion the former view is unquestionably the correct one. In the first place, the shoes are not made that give effective support; all they do is restrict movement. Secondly-, pre-school-age children are in constant movement, running and jumping about until they are tired, when they sit down. They practically never walk or stand still, and it is only then that a support might be imagined to have any effect. The risk of catching cold from going barefoot indoors in the winter is another matter, but, on the other hand, the fear of chills is undoubtedly exaggerated, dating back to the days when floors really were cold and draughty.

If pre-school children do wear footgear, then reinforced socks or special shoes with completely soft soles are the best. These restrict as little as possible the movements of the feet, and the shoes, at least, are fairly durable if they are only worn indoors and in dry weather outside. In cold or wet weather, sturdier shoes and boots are of course necessary.

The aim of the treatment of foot defects in children of preschool age should be to achieve feet of normal appearance that function efficiently. However, the treatment will either fail or will take a very long time if it is based on the routine system of prescribing arch supports and high boots that used to be so common.

Minor postural defects in the feet of pre-school children require no treatment other than the prophylactic measures described above. This is also true of more pronounced defects during the first years of life. Special exercises are scarcely practicable at that age; nor are they necessary, since an otherwise healthy child will get the right exercise by himself if he is left alone.

Four- to seven-year olds with graver foot defects should be made to do suitable exercises, preferably daily, in addition to the prophylactic measures. The programme should include the following: instruction in correct standing and walking, tiptoe exercises, grasping marbles and pencils with the toes, skipping, etc. If the exercises are to be truly effective, it is often necessary to have a trained gymnast to instruct the mothers and children. It is sometimes helpful to give the exercises in the form of rhythmic

dancing to music, which makes them more attractive to the children. In my practice I have for many years been treating my patients along these lines with very good results. In some cases of even grave postural defects, a complete cure has been effected by going barefoot consistently for a single summer. The good effect on school children of the gymnastic treatment has, in my opinion, been proved by the results of experiments on elementary school children published in *Acta Paediatrica* in 1942. Of 40 severe cases given foot exercises daily for six to seven weeks, 31 were cured and 9 improved.

At this point a few words may be included on the treatment of weak feet in childhood with arch supports. My view on this form of therapy has been influenced by the leading German orthopedists, e.g. Spitzy, Hohman, Schede, Lange, Fränkel, Thomsen, Wilhelm, Schüller, Eckhardt, et al.

Flat feet can never be cured by treatment with arch supports alone, for the muscles that are intended to hold up the arch are cut off from their function by arch supports and similar measures. Sparing the already weak muscles only weakens them further. In addition, the circulation in the foot is impaired by the pressure on the arch. Lange made it quite clear that it is fundamentally wrong to prescribe arch supports for children without at the same time seeing to it that strengthening foot exercises are carried out energetically. If the exercises cannot be performed or if they are neglected, then arch supports should not be used. Exercises are obviously out of the question in the first years of life and supports should therefore not be prescribed. Even in older pre-school children, it is doubtful if supports are ever needed. In any case, the greatest restraint should be practised in prescribing supports. At best they are of practically no use, because it is only when the child is standing still or walking slowly that they can be imagined to give any support and if small children are brought up as they should be, they very seldom either walk or stand. In short, arch supports generally do more harm than good in pre-school age children.

Finally, I should like to describe briefly the footwear most suitable for children. Stockings and socks should, as mentioned

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above, be made to fit the foot with their greatest length at the big toe. The ordinary stockings with their apex in the center may, particularly if they are on the small side, press on the toes and squeeze them together. The resistance of the stockings to the spreading of the toes is of greater importance than is yet realized. It is of great importance to the health of the foot that the toes retain from the first weeks of life their ability to spread out. It is especially important that the big toe can be spread, since the abductor hallucis muscle plays an active part in maintaining the long shape of the arch. — Hitherto no stocking manufacturer in Sweden has been willing to start making stockings shaped differently for the right and left feet, but I am convinced that it will not be long before stockings to fit the feet will be just as much taken for granted as left and right shoes are now.

For the first few years after the child has learned to walk, the best garment for indoor use is a sock knitted to fit the foot, with a piece of chamois leather or velvet sewn into the foot to prevent falling on slippery floors. Soft children's shoes can also be used. These were first described by Thomsen and have been manufactured in Sweden since 1939, when the idea was taken up at my suggestion. During the course of the years a number of models with semi-soft soles, high laced uppers, heels, padding in the soles, etc. have come into the market and completely distorted the original idea. Many of them, too, are more harmful than the ordinary stiff shoes.

The stiff shoe should meet the following requirements: 1) It should be broad enough in the toe to allow plenty of space for the toes of a healthy foot, even when they are spread out in walking. It is especially important that there be enough room inside for the big toe. This means that the shoe should be widest not over the base but over the tips of the toes. In addition, the toe of the shoe should be sufficiently high, particularly over the big toe. Many experts consider that shoes should be roomy enough to permit the wearer to flex the toes. It is advisable to have the shoe hug the heel and ankle so that it does not gape when the wearer is walking. 2) The heel should be low, at the most one centimeter high, and should not continue too far forward. Nor

should it extend too far backward, but should finish well within the limits of the upper. Some types of shoe require no heel at all. The healthy foot is created to be used without shoes and should not function on a sloping plane. In my opinion, the only justification for the heel is to increase the durability of this exposed part of the shoe. 3) The sole should be pliable enough not to prevent or make difficult the proper movements of the foot in walking. The shank should be pliable enough not to prevent the elevation of the arch and the depression of the heel in the act of walking. Thus the steel shank is entirely unsatisfactory. 4) The whole shoe, including the sole, should be made of leather, not rubber, since the latter material prevents cutaneous respiration.

Summary.

It is claimed that the prophylactic treatment of the pedal defects so common nowadays should aim to encourage the general development of the whole musculature, to lessen the strain on the feet imposed by modern living conditions and to avoid the harmful effects of restricting footgear. A form of active therapy, based on exercises to strengthen the foot muscles which should be carried out in the pre-school years is also described. The limited value of arch supports and the most suitable footwear for pre-school children are discussed.

On Injuries to Children, Caused by Corrosive Poisons.

By

BERTIL LINDQUIST and BERTIL ROOS, Lund.

The authors render an account of the children who have been injured by acid or alkali, observed in the course of a 10-year period at the Lund Hospital. The case-material comprises 44 cases, 14 of them with injuries to the eyes. Of the last-mentioned, 12 had been injured by alkaline agents (10 of them with lime) and 2 by acids (25 % nitric acid). In one case a mistake had occurred by accident at the hospital between lapis and nitric acid in Credé's prophylaxis. In all eye cases the conjunctiva and the cornea had been injured, and in 4 cases there occurred corneal opacity, but fortunately the injury in these cases was only one-sided.

The remaining 30 children had taken the injurious remedy per os, viz. in 7 cases acid and in 23 cases caustic. The age of these children was in 28 cases below 4 years, and in 2 cases over 4 years. Injuries of the nature here in question occur thus usually in early childhood. Of those children, who had been injured by acids, 2 had taken chloric acid and 5 acetic acid (about 30%) or acetic spirit (about 12%). In one case the child, dosed with the wrong medicine by her mother had been given 1 tea-spoon of concentrated hydrochloric acid instead of cod liver oil, the other injuries had been caused in play. The injuries were of a passing nature and all were discharged free from symptoms. The average time for observation is $6\frac{1}{2}$ years.

Of those children who had been injured by alkaline agents, 19 had taken concentrated (about 30 %) lye (solution used for the cleaning of milk-cans at farms). The 4 remaining ones have been injured by other substances with alkaline action. In the last-mentioned 4 cases the injuries were of a passing nature, and all were discharged free from symptoms. The average period of observation was 4 years. - In those cases where the children had been injured by concentrated lye, the accidents had occurred in such a way that the children had been drinking out of a glass bottle, mug or lin-measure. In 3 cases the children had been licking a spoon or a ladle previously used for measuring lye. Of these 19 children 2 died as the direct cause of the accident (in one case of acute poisoning, in the other of pneumonia + bronchitis purulenta + gangrene of the lungs). A further 2 fatal cases died from complication occurred during treatment. The total number of deaths was thus 4, or 21 %. Oesophagus stricture occurred in 9 of the cases, i.e. 47 %. The first symptoms of stricture were in the majority of cases discovered within 2 weeks. In no case has the interval between the accident and the first symptoms exceeded 3 weeks. The average period of observation for those children in whom stricture did not develop, was 51/2 years. Apart from the aforesaid 2 deaths caused by complications during treatment there occurred 2 cases of mediastinitis, which were cured. Of the 5 surviving cases of stricture 2 recovered after respectively 1 and 11/2 year's treatment (period of observation after recovery respectively 4 and 91/2 years).

As regards the possibilities of prophylaxis of those injuries which have been dealt with in this synopsis, the following may be stressed. 1) The 1943 Swedish Poison Statute with stipulation regarding strong acids and alkaline agents. 2) Improved hygienic supervision of farm-yards. 3) Continues work of instruction. 4) Manufacture of and recommendation of innocuous cleaning agents (preferably neutral) in which connection a prohibition against those with a strong lye content might be enacted.

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An amino acid mixture (casein hydrolysate) as an additional food for premature infants.

By

J. HENNING MAGNUSSON.

The rearing of underweight, prematurely born infants has always presented great difficulties. Even when they receive human milk the smallest of these infants generally show no gain in weight for weeks and sometimes even for one month This fact lessens their chance of survival and causes the community extra expense on account of the longer time they must be kept in hospital. It has now been discovered that most of them, if they are given a protein which has previously been digested by proteolytic enzymes, can quantitatively assimilate this form of nourishment and put on weight at a rate almost surpassing that shown by fullterm babies in many cases. The stay in hospital is thus shortened, and the risk of infection, which is a common cause of death, is proportionately reduced. As the number of premature infants born is large, the question is one of considerable interest to the community.

¹ Magnusson, J. H.: Svenska Läkartidningen, 41, 1041, 1944. — Nature, 154, 91, 1944. — Acta Paed. 32, 599, 1940. — Jorpes, J. E., Magnusson, J. H. and Wretlind, A.: Lancet, 1946, p. 228.

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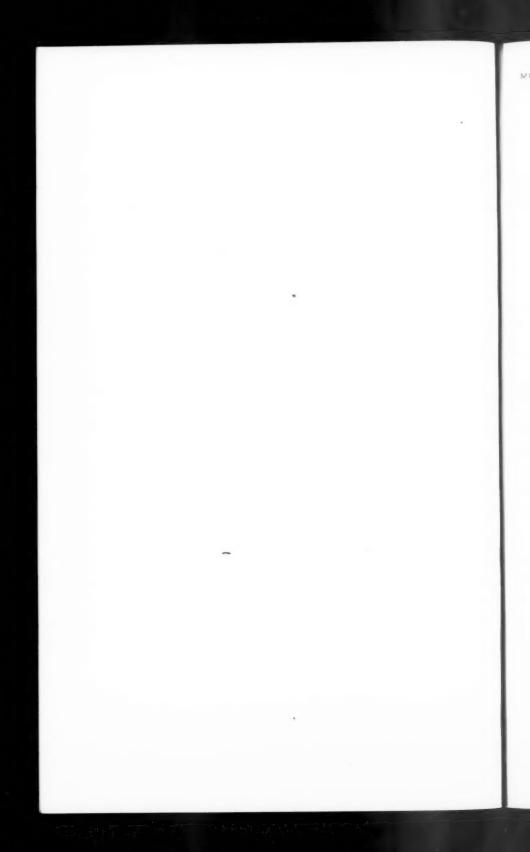
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ACTA PÆDIATRICA

EDITORES:

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EDITOR PROFESSOR A. LICHTENSTEIN
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ACTA PÆDIATRICA





FROM THE PEDIATRIC CLINIC OF THE CAROLINE INSTITUTE AT KRON-PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM HEAD: PROFESSOR A. LICHTENSTEIN

OBESITY IN CHILDREN

A CLINICAL-PROGNOSTICAL INVESTIGATION

BY

HANS-OLOF MOSSBERG

ACTA PAEDIATRICA, VOL. XXXV, SUPPLEMENTUM II

Stockholm 1948

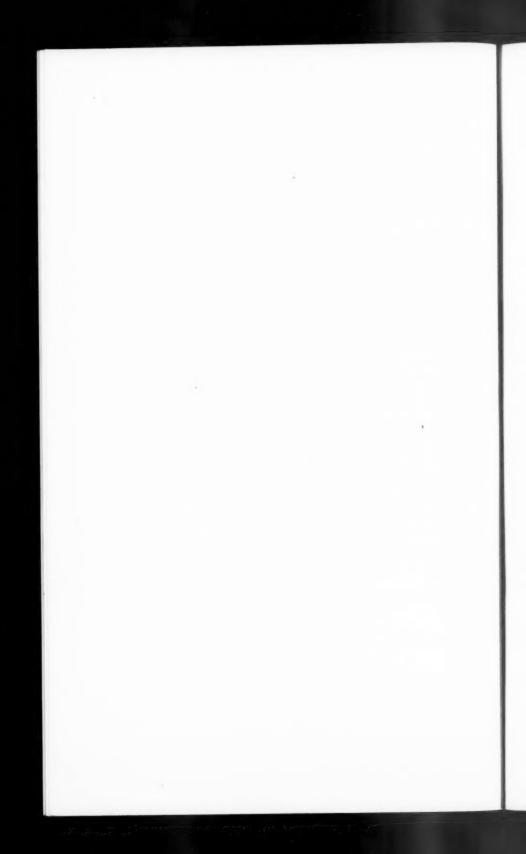
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PREFACE.

The present work has been carried out during the author's service as assistant at the Pediatric Clinic of Kronprinsessan Lovisa's Children's Hospital in Stockholm under Professor Adolf Lichtenstein. It is with deference and admiration that I hereby beg to express my great indebtedness to him for his valuable advice and helpful criticism and for all his interest extended during the realization of the work.

To Docent Leonard Goldberg I wish to extend my sincere thanks for valuable discussions in the statistical treatment of the material.

To the Heads of the other Children's Hospitals of Stockholm, Professor Arvid Wallgren, Professor Nils Malmberg and Docent Henning Magnusson I beg to convey my sincere thanks for their readiness in placing their clinical material at my disposal.

I also desire to thank Docent Urban Hjärne, Chief Doctor of the Elementary Schools of Stockholm, for placing the health records of the children at my disposal.

Part of the investigation on the relationship between hypophysis and sella turcica has been carried out at the Anatomical Institution of the Caroline Institute. For the courtesy in placing the resources of the Institution at my disposal I beg to render my thanks to its Head, Professor Ture Petrén.

The material for the determination of the normal size of sella turcica has partly been obtained from the X-ray Department of the Serafimer Hospital by the courtesy of its former Chief, the late Professor Erik Lysholm.

For stimulating discussions in the appraisement of the roent-genograms of sella turcica and of the skeletal development I wish to thank the Roentgenologist of this Hospital, Dr. Folke Ulfsparke.

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Finally, I wish to express my heartfelt thanks to my wife for her incessant and inspiring interest and her excellent secretarial assistance.

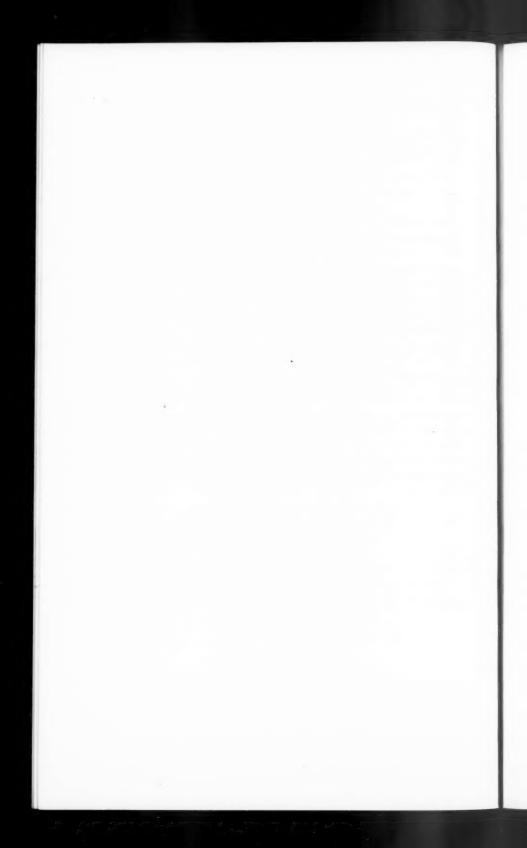
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Stockholm in April 1948.

HANS-OLOF MOSSBERG.

INTRODUCTION.

As a student and auscultator at Kronprinsessan Lovisa's Children's Hospital during 1942 and 1943 the author observed how numerous cases of obesity were admitted to the hospital for investigation, were discharged, and disappeared from view. The further course was generally unknown. This furnished the impulse to an analysis of the obesity material of the hospital and to a follow-up investigation. The enormous literature on obesity showed that opinions were considerably divergent on many points and that the problem in other particulars was inadequately investigated. The conclusions in the literature were in the majority of the cases drawn from small materials (< 100 cases). It therefore seemed of value to obtain the results from a large series of obesity cases. Thanks to the courtesy of the chiefs of all the children's hospitals of Stockholm the author was afforded the opportunity of studying the cases of obesity in their records. The entire material thus came to include more than 500 cases. The results of the analysis and the follow-up investigation of these cases are presented in this paper. The case histories of the material are deposited at the library of the Caroline Institute, Stockholm.



CHAPTER I.

Review of literature.

A. History.

Studies on obesity, published during the 17th and 18th centuries were fundamentally built on Galen's doctrine of the four humours. According to Immermann (1875) these early studies consisted of isolated case reports of extreme obesity, or discussed the dangers connected with this condition.

Not until the advance of modern physiology in the 19th century did the discussion relative to the problem of obesity break new ground. Through J. v. Liebig's experiments on the animal production of fat (cit. Immermann) light was shed on the fundamental laws of animal metabolism, and it was demonstrated that the production of fat was a general function of the organism.

Since the last decades of the 19th century and up to the present day numerous studies on obesity have been published. During the conclusion of the 19th century and the three first decades of the 20th century the discussion, especially in the German literature, predominently treated the metabolism in obesity and the exogenous or endogenous (constitutional) etiology of obesity (v. Noorden, J. Bauer, and others). Also in the English (American) literature there were advocates of the endogenous (constitutional) conception (Newburgh, and others). An endocrine (hypophyseal, thyrogenous, gonadal, etc.) etiology was considered present only in a small number of cases of obesity. An exception with an endocrine pathogenesis (adenoma of the hypophysis) was the adiposogenital dystrophy described by Fröhlich in 1901.

Since the advent of modern endocrinology and the great advances of hormone research in the thirties, a number of papers on obesity have been published both in the German and especially in the American literature, in which the cases have been classified according to *endocrine* symptoms (ZONDEK, POGGIO, and others).

Obesity in children was during the 19th century described in isolated cases by various authors. The first case which was studied in detail was published by Magnus-Levy in 1897. Since then, especially in the late twenties, a number of studies on obesity in childhood have been carried out, usually, however, based on small series (10—50—200 cases). Similarly as in the case of adults, the genesis has variously been considered exogenous, endogenous-constitutional (Chiari, Newburgh, and others) and endocrine (Rony, Nixon, Dorff, Gordon, and others). A number of exhaustive studies of recent years, especially by Hilde Bruch, New York, seem to indicate that obesity in childhood is not preponderantly an endocrine problem.

B. Classification.

The classification of obesity into various types has, as has been seen from the history, been divergent, differing in various periods of time and in the various authors. The advocates of the exogenous and endogenous-constitutional conception have considered that a constitutional predisposition is present in both but have explained the factor differently. In the exogenous group also there is thus familial obesity in approximately the same frequency as in the constitutional group. The border-line between the two groups was considered vague (v. Noorden 1900, Lyon 1910, J. Bauer 1929, and others). In the opinion of these authors there are but few endocrine cases (v. Noorden 2.7 %, J. Bauer 2.6 %).

The supporters of the preponderantly endocrine etiology of obesity (Zondek 1926, Poggio 1929, Gordon 1937, and others) proceeded, in their classification, partly from more or less subjective opinions regarding the appearance of the patient, such as the regional distribution of fat, the distribution of hair growth, etc., and partly from the results of diverse clinical investigations (basal metabolism, glucose tolerance test, skeletal development, etc.). The obesity was termed according to the hyper- or hypo-function of the supposedly fat-inducing endocrine gland, thus hypothyroid,

.

hyper- or hypo-pituitary, etc. (Shapiro 1929, Eidelsberg 1929/30, Rony 1932, Nixon 1934, Dorff 1936, Gordon 1937, Gill 1938).

A special type of endocrine obesity in adults is the picture described by Fröhlich in 1901, adiposogenital dystrophy. In FRÖHLICH's classical case the causative agent was a hypophyseal tumour. This type is characterized by obesity with a distribution of fat on chest, abdomen, hips, thighs, and mons veneris, associated with hypogenitalism, retarded statural growth and skeletal development, and low basal metabolism. Erdheim (1904, cit. Lyon 1910) described the same picture of disease in tumours of the pedicle of the hypophysis. In those cases the hypophysis was intact. The hypophyseal etiology of the disease was questioned. Bailey (1922, cit. RACHMANN 1934) advances the opinion that adiposogenital dystrophy is not due to a lesion of the pituitary but to a lesion of the hypothalamus. Leschke (1930) could at autopsy in 65 out of 145 cases of adiposogenital dystrophy not find any changes of the hypophysis but, on the other hand, lesions in the nerve fibers of the diencephalon in all of the cases. In 63 cases there were changes both in the hypophysis and the hypothalamus. This was considered to suggest a nervous regulatory mechanism in the arisal of obesity. In order to shed light on this question animal experiments are performed by many authors (first by Aschner 1912, cit. Smith 1930). By experiments on rat Smith (1930) was able to show that hypophysectomy leaving intact the hypothalamus does not produce obesity, while, if the diencephalon is injured - with or without coincident hypophyseal lesion — obesity usually results.

In boys a Fröhlich-like adiposity frequently is encountered by Shapiro 1929, Ellis & Tallermann 1934, Bornhardt 1936, Dorff 1936, Selander 1937, Bruch 1939, and others. By these authors no hypophyseal tumour was found and the prognosis was considered favorable. Dzierżyński described 1939 5 cases of adiposogenital dystrophy in boys with diffuse obesity in the mother. As etiologic he assumed, owing to a similarity of sella turcica in mother and child, a constitutional maldevelopment of the hypophysis.

The lesions in hypothalamus described above have, according to Nixon (1934) given rise to the assumption that the nervous

system plays a more important rôle in the control of obesity than do the endocrine glands.

Brain diseases, such as tumours, encephalitides, hydrocephalus, etc. are occasionally accompanied by a sudden increase of weight. The obesity (*cerebral*) in these cases usually has the adipose distribution of the hypophyseal types and is in children generally associated with mental retardation (Bergmark 1932, and others).

Obesity in *pre-adolescence* is frequently denoted as a special type (Bauer 1929, Chiari 1938, and others). It is characterized by a distribution of fat similar to that in adiposogenital dystrophy. Chiari considers this obesity a prolonged period of "der zweite Fülle", which normally occurs at the age of 8 to 10 (Schlossmann in Pfaundler & Schlossmann: "The diseases of children", Vol. II 1935). The obesity in these cases is considered to regress subsequent to puberty.

C. Heredity.

Heredity in obesity in man.

Already in 1850 Chambers (cit. Davenport) described pedigrees in which obesity had been present in several generations and also such pedigrees in which the skipping of a generation could be established. The literature on heredity in obesity has since then become voluminous. v. Noorden in 1900 established that obesity in many families has been observed so frequently that a true heredodiathesis has been accepted. In the literature the frequency of familial obesity has been reported very divergently: Bouchard 46 %, Brugsch 40 %, Lichtwitz 50 %, v. Noorden 70 %, J. Bauer 90 %, Gigon 90 % (cit. Hanhart 1940). There is general agreement on the heredodiathesis of obesity, but opinions are divided as to whether it is endogenous or exogenous in character.

The exogenous concept of v. Noorden (1900) is that the ways of living (tendency towards luxus consumption, indolence) are inherited. v. Noorden's opinion is supported by Lichtwitz, M. Labbé, Joslin, and others.

The advocates of the endogenous conception (v. Bergmann, Falta, J. Bauer, Newburgh, and others) consider the specific

predisposition towards abnormal fat deposition to be hereditary, this being assumed to give rise to a disturbance of the energy metabolism (J. Bauer 1929). They consider, however, that certain cases may be exogenous but that the exogenous-endogenous border-line is indefinite and very difficult to determine. This was already in 1910 pointed out by Lyon. Gigon (1928) even goes so far as to question the occurrence of a purely exogenous type of hereditary obesity.

A certain support for the endogenous nature of obesity is afforded by Gulick (1922), Liebendörfer (1923/24), and others.

Gulick personally belonged to a "non-fattening" type and carried out tests upon himself with diets of various caloric content, all the while performing about the same amount of work per 24 hours. In 14 months he gained approximately 12 kg in weight on a marked luxus consumption (3480—4113 cal per 24 hours), and in 3 months returned to his original weight on a slightly restricted normal diet (1874—2781 cal per 24 hours). His normal diet was approximately 2700 cal per 24 hours. His basal metabolism was normal during the entire period. On the basis of this Gulick considers that the regulation of weight is not due to an inherited change of the thyroid function.

Liebendörfer investigated 25 obese individuals, from Tübingen in Germany, during the famine years following World War I. He could not establish any exogenous factors, such as indolence or luxus consumption. In all of the 25 cases there was a family history of obesity and in the majority of the cases one of the parents was obese also. There was a female predominance and approximately one-half of the siblings were obese. Reports as to weight and height were lacking. In occasional cases, in which a generation had been skipped, Liebendörfer considers that the predisposition probably was present but that the meagre diet had not allowed the development of obesity.

Only in a small number of the investigations has the heredity been subjected to statistical treatment. The studies of Davenport (1923) and Gurney (1936) only will be cited here.

DAVENPORT in an exhaustive work studied the offspring of parents with similar and with disparate bodily build. The material

comprised several hundreds of cases, in which the bodily proportions (weight, chest measurements, etc.) of the majority of the members of the family for at least 3 generations were known. On the basis of his investigations Davenport considers that several dominant factors cause obesity and that the absence of these or the presence of recessive factors cause leanness. He points out the well known fact that some families show a large number of lean members, while other families, although usually not throughout, have a majority of plump or even obese members. The hereditary factor, according to Davenport, consists of the constitutional divergencies in appetite and in the rate of basal metabolism of the body.

Gurney's investigation comprises two groups of females, one obese group (75 cases) and one non-obese group (55 cases). The reports in regard to the obesity are partially based on subjective evaluations, this depreciating the value of the investigation. Notwithstanding this, the result is in entire agreement with the results of Davenport and the conclusions drawn by the authors are similar.

In man there is thus very probably a hereditary obesity but this is not proved. It has not been possible to distinguish between the hereditary factors and the influence of the surroundings. In animal experiments, however, this has been feasible and by this method valuable information has been obtained.

Animal experiments on heredity in obesity.

In 1925 and 1927 Danforth described a yellow, previously known, mouse strain with obesity, and showed that the yellow colour and the disposition towards obesity are inseparable. The author's conclusion that both of these qualities are bound to the same gene (A^y) seems to be correct. When mice with the A^y gene and mice without the A^y gene were placed on the same feed the animals with the A^y gene gained more in weight and became obese. When deprived of feed the animals lost weight parallelly. In a number of normal mice, without A^y gene, a weight very similar to that of the yellow mice was obtained on removal of

both of the ovaries. This suggests, according to Danforth, that parts of the endocrine system possibly may participate in the surfeit accumulation of fat. He also believes that there possibly may be a nervous regulatory factor.

M. Weitze (1940) performed a series of accurate investigations on an obese yellow mouse strain, with, inter alia, parabiosis experiments. In these experiments the vascular system of yellow obese mice was coupled to the vascular system of normal mice with the result that both animals showed a normal weight. If the connection was broken off both animals developed according to their normal disposition. Parabiosis experiments between two normal mice or between two obese mice had no effect on the development of the animals either in a normal or in an abnormal direction. Weitze considers that the cause of the obesity through these experiments has been shown to be of hormonal nature, which is a conceivable explanation.

On continued experiments with hypophysectomized obese mice Weitze observed an increased insulin tolerance at normal values for blood sugar and hepatic glycogen. She considers this to show the probable presence of an abnormal secretion of hormones of importance for the carbohydrate metabolism. As Weitze's obese mice when allowed unrestricted feed consumed 10 % more than did the normal mice this conclusion may possibly not be correct. A rise in insulin tolerance, possibly hormonally determined, is, as a matter of fact, normal on a luxus consumption of carbohydrates (Himsworth 1934, and others). The possible hormonal cause thus still seems to be obscure.

Animal experiments on obesity show that obesity in the yellow mouse strain is dominant hereditarily and possibly is due to a hormonal disturbance.

D. Physical and mental development in obesity.

Age at the onset of obesity.

Already Immermann (1875) pointed out that obesity debuts in children at 1 year of age and in adults especially after the age of 40.

Obesity in children frequently debuts at the ages of 0 to 4 and 7 to 11 (table 6 p. 50). No sex-linked difference is found (Bruch 1939 a). The two peaks for the onset of obesity are considered by a number of authors (Ellis & Tallermann, Chiari) merely as an unduly marked manifestation of a normal reaction. This is due to the fact that in childhood the conditions are specific as physiologically there are obese periods at the ages of 1 to 4 and 8 to 10 (Schlossmann, Chiari, and others).

Initiating causes of obesity.

Since of old the connection between the onset of obesity and gravidity and the climacteric period has been observed. The predisposition of certain children towards obesity in puberty has since long been recognized. The connection between obesity and cerebral lesions was pointed out above. Diseases of the brain subsequent to which obesity arose were especially chorea, encephalitides, tumours and hemorrhages.

The arisal of obesity subsequent to non-cerebral diseases has also long been known. Lyon (1910) expresses the opinion that alcoholism, syphilis, rheumatism, trauma, nervous chock, etc., are the primary cause of a number of cases of obesity.

Many authors, especially in the thirties (RONY 1932, GURNEY 1936, GORDON 1937, GILL 1938, BRUCH 1940) supported this opinion and described cases in which the obesity debuted following infectious diseases such as morbilli, typhoid, and pertussis; following operations such as tonsillectomy and appendectomy; subsequent to trauma and its sequelae such as fractures of the extremities; and subsequent to the occurrence of death in the family.

Weight at birth.

The cases of "macrosomia adiposa congenita" (Christiansen 1929) were "large and fat" already at birth. J. Bauer (1929) had in his material a number of constitutionally fat children with a birth weight exceeding $4\frac{1}{2}$ to 5 kg. Orel (1931/32) pointed out that among his series of 24 children with a birth weight exceeding

5 kg there were children whose parents were constitutionally obese. These children subsequently became obese also.

Data regarding the birth weight of obese children are in some instances reported in the literature. The data are not in agreement. Bornhardt (1936) and Gordon (1937) found that 20 to 30 per cent of the cases had a weight at birth exceeding 4 000 gm. Bruch (1939 a) on the contrary, could not in her material of 90 cases demonstrate any deviation from the normal; nor was any correlation observed between the early onset of obesity and a heavy weight at birth.

Height and weight. Rohrer's index.

In numerous instances of the reported cases of obesity in children the height has been shown to exceed that physiological for the age. Extremes among these cases are children with so called "adiposogigantismus" (CZERNY & KELLER 1928, OPITZ 1933, REYE 1935, HANSSEN 1937), in which the stature is equivalent with the development of a normal child of at least a couple of years older.

The majority of authors in their material of obesity in children have found this skewness of the height towards higher average values. Hilde Bruch in 1939(a) in her comprehensive study on the growth and development of obese children gave a survey of the literature on this subject.

There have been many attempts to define an absolute weight above which a person is obese. Critical appraisers (among others Nixon 1934) point out that the various tables of height and weight often neglect individual variations in build and constitution. No definite weight limit, above which a child or an adult may be considered to suffer from obesity, can therefore be set.

On the basis of Swedish children in the ages 1 to 20 years weight and height tables are compiled by Broman, Dahlberg & Lichtenstein (1942). The material is treated statistically and the variations for different ages specified. In a section of the study Dahlberg performed a computation on the same material according to Rohrer's index (Rohrer 1908), "height-weight-index of build". The index computation can according to Pfuhl (Peter, Wetzel & Heiderichs Handbuch der Anatomie des Kindes 1928—1938)

not be used to determine the status of nourishment but may, however, be employed in following the bodily development. Rohrer's index is computed according to the formula:

$$I = \frac{\text{weight in gm}}{\text{(height in cm)}^3} \times 100 = \frac{W}{H^3} \times 100.$$

Rohrer's index applied to the Swedish material shows for both boys and girls that index commences by falling rapidly, remaining fairly level after the age of 7 to 8. At 13 to 17 the index in regard to the girls rises somewhat, again remaining fairly level after the age of 17.

No investigation on Swedish adults according to Rohrer's index has yet been published.

Growth of the normal child in puberty.

Boas in 1930 showed (cit. Lewis 1936) by yearly studies of weight and height in normal children that the children in whom puberal growth acceleration occurs early, i. e. at 11 to 12 years, have a total growth period of shorter duration and greater intensity than those children in whom puberty occurs later. The growth period for these latter is drawn out over a longer period of time. This was later clearly illustrated by diagrams in Shuttleworth's monography 1939 (cit. Greulich 1941). It appears from the author's diagrams that children with the greatest increase of height at an early age as adults have a lesser absolute height than children with a slower development. This tendency is found in boys as well as in girls. Shuttleworth in a monography 1937 (cit. Greu-LICH 1941) also shows analogous conditions in girls with early and with late menarche. In agreement with this Simmons & Greulich (1943) found the absolute body height in the pre-menstrual years to be greatest for girls with an early menarche.

In Shuttleworth's monography (1937) is included a diagram showing the yearly increment in growth prior to and subsequent to menarche. According to Simmons & Greulich (1943) this is greatest in subjects with an early menarche. In these cases the greatest yearly increment in growth occurs in the year preceding menarche,

while in cases with a late menarche it occurs 2 years prior to menarche. The acceleration of growth in puberty debuts (Shuttleworth) 2 to $2\frac{1}{2}$ years prior to menarche and 4 to 5 years following menarche growth is terminated. In Swedish girls the onset of growth acceleration according to Broman, Dahlberg & Lichtenstein's height tables occurs $2\frac{1}{2}$ to 3 years prior to menarche (normal menarcheal age barely 14 years, cf. p. 56) and 4 to 5 years after menarche growth is usually completed.

Analogous with this, also, an acceleration in the yearly increment in weight occurs in pre-puberty. The period of time during which this acceleration takes place is, however, longer than the correspondent period for the acceleration in yearly increment in height.

This is relative to normal children. There is thus a physiological increase of height and weight in puberty ("Periode der zweite Fülle"). Several authors (Ellis & Tallerman, Chiari, and others) consider cases of obesity in this period, the so-called pre-puberal obesity, as more or less physiological and as having a favorable prognosis.

Puberty in obesity.

The development of puberty in obese children has been subject to much discussion. Reports of early as well as late puberty are numerous. Particularly obese girls and their menarcheal age have been studied and an early menarcheal age has been established by a number of authors (Ellis & Tallermann 1934, Bornhardt 1936, Hering 1938, Nobécourt 1938, Bruch 1941).

In obese boys the often Fröhlich-like distribution of fat and simulating or true hypogenitalism earlier gave rise to the opinion of a late puberal development (Enke in Hanhart, Lange & Just: Handbuch der Erbbiologie, Bornhardt 1936, Hering 1938, and others). This opinion was based on findings from isolated cases. Nobécourt (1938) however, on the contrary found in his material a normal sexual development in 46 obese boys and in some cases even an early development.

Bruch (1941) studied puberty in more than 200 obese children. She divided the girls in 4 groups: those without signs of puberty, those with beginning puberal development (changes of the papillae,

development of breast and pubic hair), those with advanced puberty, and those with conclusion of puberal development. Bruch for the normal menarcheal age applied Boas' normal curve, based on 226 non-Jewish American girls and Engle & Shelesnyak's study on 250 girls of Jewish extraction. Both of these materials indicate 13 to 13½ years as maximum for the distribution curve of the menarcheal age. In regard to obese girls the correspondent maximum in Bruch's material was at 11½ to 12 years.

In obese boys Bruch for comparison with the normal material used Schonfeld's third stage (unpublished studies). This stage corresponds with a certain development of the genitals and the pubic hair. The case distribution for this group of normal children shows a maximum at 12 to 13 years. The maximum of the obese boys in Bruch's material occurred at the same age. Thus, nothing speeks for a late puberty in obese boys.

Bruch's conclusion was: "Early puberal development is the rule for obese girls and is not unusual for obese boys".

Development of intelligence in obese children.

The mental development of obese children has not been subject to much interest in the literature. A few authors have observed some mental retardation (e. g. Rony 1932 in 8 out of 50 cases) but the reports are usually based on small series.

Shapiro (1929) pointed out in an investigation on "High School Boys" that 48 boys in the age of 12 to 19 years with adiposogenital dystrophy at some period of their growth had had a transient mental retardation, and were therefore 2 to 3 years older than their school-mates in the same grade.

HILDE BRUCH (1940) has devoted especial attention to the mental problems in obesity in children. The mental development, as expressed by the intelligence quotient; she considers to be frequently advanced.

E. Basal metabolism in children.

Normal children.

The literature on basal metabolism in normal children is enormous and only a number of the most important studies of recent years will be mentioned here.

The result of the investigations in the literature have — especially earlier — been widely divergent. The discrepancies may often be explained by the differences in technic and evaluation. Disparities in the experimental conditions, e. g., whether the child is awake or asleep, during the determinations, whether only the first test is included, etc., may account for divergencies. The basis for determinations used have been calories per hour referred to weight, to height, to age, or to total body surface, and calories per hour per kg body weight, per cm height, or per square meter surface area all referred to age.

In the exhaustive works published by Lewis, Kinsman & Iliff (1937) and by Lewis, Duval & Iliff (1943 a, b, c) the normal values of the literature have been tabulated and compared with the very large normal material of the authors. This comprises 1007 BMB determinations on 70 American boys and 718 determinations on 57 American girls in the ages 2 to 15 years.

The investigations of Lewis et al. will be cited briefly: Methodics: The open circuit apparatus according to Higgins & Bates was used and repeated determinations were done on each child, usually at 3 months intervals. The children were awake and fasting during the determinations which were done in the morning. They were taken to the hospital by car and were rested there at least 20 minutes prior to the test. The surface area was computed by the Du Bois' height-weight formula according to the nomogram of Boothby & Sandiford (1920). Results: The lowest coefficient of variation (approx. 6%) was found for calories per hour referred to weight and total surface area, and for calories per hour per square meter referred to chronologic age. For these and for calories per hour referred to height normal standards were established (J. of Pediat. 23: 1, 1943).

For the Lewis et al. standards (1943 c) for weight, for total

surface area and per square meter surface area 95 % of the values $(M\pm 2\,\sigma)$ fall within the limits \pm 12 % of the standard values, and 99.7% $(M\pm 3\sigma)$ fall within the limits \pm 18 %. Correspondent figures for the height standards show a dispersion which is 2 to 4 % greater. The authors state clearly that their values only are valid for normal children with certain defined maximum and minimum values for weight, height and surface area, and that until further but little can be said in regards to the choice of standards for children with abnormal body proportions.

Lewis et al. have done a comparison between the open circuit and the closed circuit methods of basal metabolism determination. On determinations on the same child with both methods they found entirely comparable values, on the condition that the subject was in a post-absorbtive state, and well relaxed, and that a careful technic was observed.

BOOTHBY, BERKSON & DUNN (1936) consider the training to play a certain rôle for the BMB values and they therefore use only the first value obtained. Lewis et al. have compared the two first BMB values of their series and can not show any significant difference which may be attributed to the training.

The values of Lewis et al. expressed in calories per hour referred to weight, to height and to surface area are in good agreement with the most important investigations on this subject of the literature. Their values expressed in calories per hour per square meter are, on the other hand, lower throughout.

The values of Bierring, Nylin, Kestner & Knipping, de Bruin, and others are entirely comparable with the standards of Lewis et al. The normal variations of these authors lie within approximately ± 17 %. The results of certain other investigations, e. g. Topper & Mulier are somewhat divergent from the values of Lewis et al., but this may at least to some extent be due to the selection of the material or to differences in the bodily proportions of the material. The values of Talbot and his co-workers (1937, 1938) are to some extent lower, due to the circumstance that these authors permitted the children to sleep during the investigation. Values exceeding those of Lewis et al. were, inter alia, obtained by Boothby & Sandiford (1921).

Basal metabolism in puberty.

The question of the influence of puberty on the basal metabolism has been the subject of many investigations and opinions have been divergent. The majority of the authors have proceeded from the determination of calories per hour per square meter surface area referred to age. Some of these, Du Bois (1916), Topper & Mulier (1932), Nylin (1935), and others, have found an absolute increase in basal metabolism as an expression of increased metabolism in puberty. On the other hand Bierring (1931), Bruen (1933), Boothby, Berkson & Dunn (1936), and others, consider the increase to be relative only in that the annual decrease of basal metabolism expressed in calories per hour per square meter is less marked. Some earlier workers, Benedict & Talbot (1921), and others, have not been able to establish any change whatsoever.

The material of Lewis, Duval & Iliff (1943 d) treated from this point of view shows that the annual slope in basal metabolism expressed in calories per hour per square meter decreases during puberty in boys as well as in girls. This is in agreement with the results previously obtained by Bierring, and others mentioned above.

The Child Research Council of the United States (cit. Lewis et al. 1943 d) establishes the average onset of puberty in American children at the age of $12\ ^3/_{12}$ years for boys and at $10\ ^7/_{12}$ years for girls. These average ages for the onset of puberty occur in the earlier part of that period in which the basal metabolism (expressed in calories per hour per square meter) shows a lessened decrease. For the children in pre-puberty the basal metabolism is thus proportionately higher during that period in which the secondary sex characteristics commence to appear.

Obese children.

The total heat production of obese subjects is in adults as well as in children higher than that of normal individuals of comparable ages (Bruch 1939, Newburgh 1944, and others). Bruch assumes that this in obese children primarily is due to the greater height of these children in comparison with the height of normal children of comparable ages.

There has in the literature been much discussion as to whether the BMB values of obese children are to be expressed with reference to weight, to height, or to surface area. Agreement has on this subject not been reached.

Talbot, Wilson & Worcester (1937) used Talbot's weight and height standards on a group of moderately overweight children (+ 20–33 %; 53 cases; 8–18 years) and on a group of very obese children (+ 33–80 %; 12 cases; 5–15 years). With reference to the weight standards they found a basal metabolism of -4.4 % and +1.1 %, respectively, and with reference to the height standards a basal metabolism of +8.7 % and +25.7 %, respectively. The difference is thus great with reference to the height standards, which suggests an increase in active heat productive tissue at increasing overweight. The difference with reference to the weight standard is insignificant.

Bruch (1939b) came to the same results as Talbor et al. She further found in her series of 72 cases that the energy metabolism showed lower values when referred to the body surface standard of Boothby & Sandiford than in comparison with the weight standard of Talbot. The standards of Boothby & Sandiford and those of Talbot are, however, based on values from different materials and obtained under different conditions and are thus not entirely comparable.

The concepts of fat as heat-producing tissue are divergent. Topper & Mulier (1929), Evans & Strang (1929), Talbot (1938), and others consider the adipose tissue to be entirely "inactive", while others in agreement with de Bruin (1939) ascribe to the adipose tissue a certain limited "activity". Bruch cites Schoenheimer's (1937) study with heavy hydrogen, which establishes that all fat deposits are very actively involved in the processes characteristic to life. To which extent this holds true with regards to the enormous fat deposits of the obese individual is, however, not known.

Talbot, de Bruin, and others call attention to the increase of musculature necessary to carry the fat. This factor increases the amount of heat productive "active" tissue and the total heat production per 24 hours is, in fact, higher in obese children than in normal children of comparable ages.

F. Glucose tolerance.

Since in the early twenties the micromethods for the determination of blood sugar have become common knowledge a voluminous literature on the glucose tolerance in man has appeared. The main traits of normal conditions seem to be fairly well known but the conditions in obese individuals and especially in the obese child are as yet imperfectly illuminated. A number of the most important studies on this subject will here be cited, but only such studies, however, as are relevant to the present investigation on the glucose tolerance in obesity in children.

Fasting blood sugar value and glucose tolerance in normal adults and children.

The normal fasting blood sugar value in children, according to the investigations of Svensgaard (1931) on 22 children in ages ranging from 1 to 13 years, is 88 mg % with a variation of 68—99 mg %. Other authors report a greater variation 60—120 mg % (cit. Svensgaard). In adults the fasting blood sugar variation is considered to be 60—120 mg % (cit. Malmros 1928). Goldberg & Luft in a recent investigation found a mean value for the fasting blood sugar in normal adults in Sweden of 95.9 \pm 2.0 mg %. The standard deviation (σ) is \pm 11.4 mg %. The variation for normal children and adults is thus generally within the limits \pm 30 mg %.

A number of factors in *peroral glucose tolerance tests* have been shown to be of importance for the course of the blood sugar curve, i. e. for the glucose tolerance.

The fasting period usually required prior to the tolerance test is 10 to 15 hours. This period of time seems to be well balanced, Rumpf (1924) having shown that a fasting time exceeding 22 hours in young children may cause a considerable fall of the fasting blood sugar value. Furthermore, Staub (1922), Traugott (1922), Malmros (1928), and others have shown that a prolonged fasting period of 48 to 72 hours prior to the glucose tolerance test gives a considerably augmented increase of blood sugar in adults.

The size of the glucose dose seems, within rather wide boundaries, to be nonessential with regard to the degree of hyperglycemia. Traugott in 1922 found that sugar doses between 20—100 gm (correspondent to approx. $\frac{1}{2}$ —2 gm/kg bodily weight) and Malmros in 1928 found that sugar doses correspondent to $\frac{1}{2}$ —1 gm/kg bodily weight give approximately the same degree of hyperglycemia. In. K. M. Hansen's experiments (1923)with very large doses \geq 200 gm, correspondent to approximately 3 gm/kg bodily weight the maximum value did not exceed 180 mg %, but the time of return, however, was longer than the normal time of return.

Accordingly, ½-2 gm glucose per kg bodily weight is an appropriate dose for peroral glucose tolerance tests.

The majority of the more comprehensive studies have been carried out with 10—15 per cent glucose solutions. Hagedorn (1921), Malmos (1928), and others have found that the blood sugar curve is not markedly influenced by the concentration of the glucose solution. Ross, however, found in 1938 that a 25 per cent solution occasionally gives rise to nausea and "erratic curves". Moreover, Beeler, Bryan, Cathcart & Fitz (1922) have shown that a glucose solution of about 10 per cent is that which is the most speedily absorbed.

Thus, a 10 per cent glucose solution seems to be the most appropriate in peroral glucose tolerance tests.

In the normal tolerance curve the blood sugar reaches the peak of the curve in rather varying periods of time, according to various authors. Labbé & Boulin (1925) report the mean time as 70 minutes and Svensgaard (1931) as 36 minutes (variation 5—110 minutes). The time of return of the curve is according to the same authors between 1 and $2\frac{1}{2}$ hours.

The course of the tolerance curve is used to determine whether the carbohydrate tolerance is high, low or normal. The methods for the determination of the limits of the tolerance have been very divergent but generally the maximum blood sugar value and the maximum rise of the blood sugar curve above resting level have been used. A maximum blood sugar value of $>170-180\,$ mg % and a maximum rise of blood sugar more than approximately 80 mg % are considered to correspond with a low tolerance and

values < 135 mg % and < 35 mg %, respectively, are considered to correspond with a high tolerance (Ogilvie, Embleton, Ross, and others). A method based on the area enclosed by the blood sugar curve has been used by Himsworth (1935/36), and others, but does not appear to offer any definite advantages.

Spence (1920/21), Malmros (1928), and others have shown that the glucose tolerance in normal adults decreases with advancing chronological age.

Already the establishment of Bang in 1913 that the glucose tolerance in rabbit is decreased by starvation and that a second glucose tolerance curve always is lower than that immediately precedent indicates the importance of nutrition for the glucose tolerance. Hamman & Hirschmann in 1919 carried out similar experiments on man and came to the same results. The voluminous literature on these questions which subsequently has appeared has been exhaustively reviewed by Himsworth (1933, 1934, 1935). This author in 1934 showed that the carbohydrate content, inter alia, of the feed prior to the tolerance test is a factor determinant for the degree of tolerance in rabbit. The greater the carbohydrate content of the feed, the higher is the tolerance, and vice versa. In 1935/36 Himsworth showed that this is valid also for normal adults and Langner & Fies (1941) later came to the same result.

Glucose tolerance in obese adults.

Labbé & Boulin showed in 1925 that the fasting blood sugar value is similar in normal and in obese individuals, but that the time taken by the blood sugar curve to return to resting level is prolonged in obese individuals. The mean time of return was somewhat more than 3 hours.

OGILVIE (1935) and EMBLETON (1938) have in obese adults shown that in these as well as in normal adults the glucose tolerance decreases with advancing chronologic age. These authors furthermore find that the glucose tolerance is not influenced by the degree of the overweight. Embleton also establishes certain sex-linked differences in his material. He finds that the males on an average have high tolerance curves in 73 % while the females have but 35 % high tolerance curves.

Labbé & Boulin, Ogilvie, Embleton, and others have furthermore shown that the age of the obesity, i. e. that time during which the obesity has been present, influences the degree of tolerance in such a manner that the older is the obesity, the lower is the tolerance. To which extent this may be due to the simultaneously advancing age has not been definitely established. In Ogilvie's investigation the age factor has to a certain extent been eliminated by the division of the cases into 10-year periods. In the material of this author the glucose tolerance appears to decrease most rapidly during the first 5 years of obesity. In cases which have been obese > 18 years, he finds no instance of normal tolerance. No analysis of the diet has been done by Ogilvie.

Glucose tolerance in obese children.

The literature on glucose tolerance in obesity in children is very scanty. The author has in the literature not been able to find any exhaustive analysis of the glucose tolerance in obese children, in which consideration has been taken to the age of the patient, the degree of obesity, the age of the obesity, the diet, etc.

Gordon (1937) reports for a series of 50 obese children a mean value for the fasting blood sugar of 89.3 mg.% which is in agreement with the normal.

The glucose tolerance in different types of obesity has been investigated by some authors. Ellis & Tallermann in 1934 found that cases of exogenous obesity have a normal or a decreased glucose tolerance and that cases of endogenous obesity have an increased or a normal glucose tolerance. Shapiro (1929), Dzierzyński (1939), and others report that increased glucose tolerance is present in adiposogenital dystrophy. Their cases, however, lacked the tumour of the true Fröhlich cases and therefore belong to the group of Fröhlich-like cases.

As was mentioned above the obesity is by various authors classified according to different "endocrine" symptoms (cf. p. 10). Rony (1932), among others, groups his material of obese children (50 cases) according to this basis. He finds in his series no significant relationship between the degree of glucose tolerance and the "en-

docrine" type of the obesity, and considers that other factors, especially cerebral, are of greater importance for the degree of the glucose tolerance.

G. Sella turcica.

The question of the size of sella turcica on the roentgenogram and its relationship to the size and function of the hypophysis has during the last twenty years been subject to much discussion within roentgenological and endocrinological circles. In this connection some authors have also touched upon the relation of sella turcica to obesity, but no exhaustive description of the sella's size in different types of obesity has ever been done.

Normal values for the profile surface of sella turcica on the roentgenogram.

The method earliest used for determination of the size of sella turcica consisted in measuring the sella's breadth and depth expressed in centimeters. The determination of size was by this method extremely inaccurate as the authors made measurements in different ways. Nor could by this method the varying form and appearance of sellas with the same diameters be expressed. According to HAAS (1925) deviations in the size of the surface might amount to as much as 25~%.

With the Haas' (1925) mm²-method a more exact procedure for measuring the size of the sella has been obtained. The procedure is as follows: The contour of the sella obtained by x-ray with a constant distance focus-film is traced on a mm-squared paper and the number of mm² is summed up. As upper limit — correspondent to the entrance of the sella — the connecting line between the lowest point of the tuberculum curve and the innermost point of the tip of the dorsum has been chosen.

Bokelmann in 1934 stressed the importance of using the *median* sella profile in order to obtain the most correct measurements possible of the sella surface. If the floor of the sella is flat there will be a sharp demarcation of the sella contour. Usually, however, it is arched. In this case an indistinct bottom contour will be

obtained in which the lower limit is correspondent to the median and the upper limit to the lateral sella profile.

A number of authors have utilized the method of Haas and have reported normal values of the size of the sella turcica in children (Steiert 1928, Sartorius 1929, Wieser 1933 and Kovács 1934). The values of Haas, Kovács and also, to a certain extent, Sartorius, hold an intermediate position among the normal curves. The curves of Steiert as well as the latter portion of those of Sartorius have a higher trend, while Wieser's curves are lower (fig. 13 p 80). In infants the literature reports mean values for the profile surface of sella turcica which are but negligibly divergent from each other.

The reports on the variation of the normal values are divergent. The distribution, irrespective of age, has been reported from $\pm~5-10~\rm mm^2$ (Sartorius) up to $\pm~25-30~\rm mm^2$ (Steiert). Intermediate between these values lies the variation reported by Haas, $\pm~15-20~\rm mm^2$. The border values for different ages have been reported by Hotz, Haas and Kovács, but none of these authors have used statistical methods of computation.

Relationship hypophysis-sella turcica.

The question as to whether there is any relationship between the size of the hypophysis and the surface of the sella turcica on the roentgenogram has been subject to much discussion in the literature. Opinions have been divided. Some authors consider acc. to Ottaviani that there is a connection (Cushing & Caselli, Barbara, Cignolini, and others), while other workers hold that this is not the case (Castaldi, Torrigiani & Vannucci (cit. Cignolini)). The normal growth curves for the profile of sella turcica and for the weight of the hypophysis, determined separately, are parallel during the period of growth. This has been considered to support the assumption of a relationship.

Investigations on the size of the sella turcica profile surface on the roentgenogram and the volume of the correspondent hypophysis have been done by Bokelmann (1934), Kovács (1934) and Otta-Viani (1938). ir

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Bokelmann's exhaustive investigation has afforded the result that there is a definite relationship in 80 to 100 % of the very small hypophyses. In Ottaviani's investigation no relationship is demonstrable. Both of these investigations are done on adults.

Kovács also has observed a certain correlation. His material (12 cases), however, is too small to allow of any conclusions. Four or five of the cases were children.

Sella turcica in obesity.

The size of the sella profile in obesity has remarkably seldom been discussed in the literature and only in small series.

Haas (1925) and Steiert (1928) consider that there is no characteristic sella picture. Haas, it is true, points out that large sellas often are present in adiposity, but neither he nor Steiert have further classified the obesity cases. In the material of Rony (1932) 17 sellas were normal, 1 "extremely small", 3 "small" and 2 "rather large and deep".

In adiposogenital dystrophy the literature as classic reports a large sella with a widened sella entrance (Erdheim & Schüller, cit. Assman). Of the 7 cases with this disease in Haas' material only 1 case shows this classical picture; 4 have an enlarged and 2 have a normal sella. Reinert (1926/27) has described a pathologically small sella (30 mm²) in one child of 10 suffering from this disease, while Steiert in 2 children found large sellas, one of which was "pathologic".

H. Skeletal development.

Skeletal development in normal children.

Skeletal development has been subject to numerous studies and an exhaustive review of the literature was published by Flory in 1936. In the present work reference will be made only to the standards of Ruckensteiner (1931), to those of Flory and Todd (1936 and 1937, respectively), and to the standards of Lurie, Levy & Lurie (1943). Elgenmark's (1946) normal standards for

Swedish children only include children up to the age of 5 and could therefore not be used in the present investigation.

The standards of Ruckensteiner which are frequently used in Sweden indicate the normal skeletal development in various regions of the body. In Ruckensteiner's report there is, however, no data on the size of the material, the national backgrounds or the social status of the children.

The standards of Flory (1936) and Todd (1937), widely used especially in the United States, assess the skeletal development of the hand and wrist only.

The Flory standards are based on $>6\,500$ determinations of skeletal development in approximately 1500 subjects. The racial background of the material is not reported. FLORY determines the skeletal age at 1 year intervals, finding the statistically computed standard deviation in children from 4 to 14 years to be approximately \pm 12 months.

Todd's material is based on a group of American children of various racial strains and from all social groups (excepting those in a state of destitution). There is no race-linked difference, but data in figures, however, are lacking in this respect. Todd determines the skeletal age at 6 months intervals and the normal variation is \pm 2 years.

It would appear from the studies of Flory and Todd that a certain experience in roentgen-diagnostics is necessary in order to give an exact assessment of the stage of development of the various skeletons.

Lurie, Levy & Lurie (1943) have prepared standards based on x-rays of hand, foot, cubitus, and pelvis. The material comprises 1 129 healthy normal white children and adolescents (704 hoys and 425 girls) in the ages of $2\frac{1}{2}$ to 19 years. The age at skeletal development is reported in standards at 1 year intervals and the normal variation is about \pm 2 years. The standards are so arranged that the lowest and the highest skeletal age may be defined. Within these limits the probable skeletal age is then determined. The method is simple and easy to use for practical clinical purposes.

In table 1 is set forth the normal age of bone development for the standards mentioned above. The values in brackets refer,

Table 1. Comparison between some of the normal standards for bone maturation. Age of the appearance of the bone centers is expressed in years.

Skeletal area	Rucken- steiner (1931)	Flory (1936)	Todd (1937)	Lurie, Levy & Lurie (1943)
		Boys		
Epiphyses of me-		1		1
tacarp	1-3(2)	2	1 3/12	$\leq 2\frac{1}{2} - 4 (\leq 2\frac{1}{2})$
All tarsals present.	ca. 3	_	_	5
All carpals present (except pisifor-				
me)	ca. 6	7	6 3/12-8 3/12	8
Epiphysis of os				
calcis	6-9 (8)			6-10 (8)
Distal epiphysis of		-	221 221	
ulna	-7 1/2 (6 1/2)	7	6 3/12-8 3/12	5-10 (7)
Olecranon process of ulna	8-10 (9)	-		8-13 (11)
or uma	0-10 (3)			0-13 (11)
		Girls		
Epiphyses of me-		1		1
tacarp	1-3(2)	2	1 3/13	$\leq 2 \frac{1}{2} (< 2 \frac{1}{2})$
All tarsals present.	ca. 3	-	_	$\leq 2 \frac{1}{2} (< 2 \frac{1}{2})$ $\leq 2 \frac{1}{2} (< 2 \frac{1}{2})$
All carpals present (except pisifor-				
me)	ca. 5	6	4 9/12-7 3/12	5
Epiphysis of os				
calcis	6-9(8)	-		5-9 (7)
Distal epiphysis of				
ulna4	1/2-6 1/2 (5)	6	4 9/12-7 3/12	4-8 (6)
Olecranon process	0 10 (0)			- 10.00
of ulna	8-10 (9)	_	-	7—10 (7)

Values in brackets in regard to Ruckensteiner standards refer to the maximum of the curve of distribution, in regard to the values of Lurie et al. to the fiftieth percentile of the appearance of the bone center in question.

with regard to Ruckensteiner, to the peak of the curve of distribution and for Lurie, Levy & Lurie to the occurrence of 50 % of the bone development in question.

The values of Flory and Todd are in their comparable portions perhaps best in agreement with the standards of Lurie et al. There is, however, no great difference on comparison with Ruckensteiner's standards.

A comparison between the standards of Ruckensteiner and those of Lurie et al. shows with regards to the girls on the whole agree-

ment for the skeletal age of development. In boys, however, the bone maturation according to the Lurie standards occurs approximately 1 year later than according to the standards of Ruckensteiner.

It appears from the table that the standards of Flory, of Todd and of Lurie, Levy & Lurie give for the both sexes essentially conformant values for the normal bone maturation.

Skeletal development in obese children.

There are in the literature but few series of obese children which have been studied with consideration to the skeletal development and in the investigations done there has been no attempt to separate the various types of obesity.

Dorff in 1935 described a group of 40 children with retarded skeletal development suggesting a "masked hypothyroidism". In 28 per cent of the cases there was presence of obesity. Dorff does not mention which normal standards were used.

PRIESEL & FREY (1938) have in their series of obese children (30 cases) found that the skeletal development corresponds to, or is somewhat advanced in relation to the chronologic age. The normal material for the comparison is not reported.

In Bruch's work (1939a) in which the skeletal maturation of 24 boys and 33 girls was studied there is a marked racial mixture. More than 50 per cent of the children are of Jewish race and the majority of the parents of the remainder originate from various European countries. The author has not grouped the cases according to the type of obesity. She has determined the skeletal age, partly according to the standards of Flory and partly to those of Todd, and finds the skeletal age of obese children frequently advanced in relation to the chronologic age. On comparison of the skeletal age with the height age (= the age of the average child at the height in question) she finds a considerably better correlation than in comparison with the chronologic age.

Bruch came to the same result in her study of 1941 (141 determinations). There is, however, no information as to whether this material was new or to some extent the same as that of 1939(a).

Talbot & Worcester in 1940 determined the skeletal age according to Todd's standards of 15 obese children with absence

of signs of endocrine disturbance. They found the skeletal development either normal or advanced. A comparison with the height age was not done.

In obese children the skeletal age thus seems to be advanced in relation to the chronologic age, while a comparison with the height age shows a better agreement.

I. Prognosis.

The obese children's development subsequent to puberty has to some extent been discussed in the literature but the conditions in adulthood (> 20 years) have, as far as has been established by the author, but imperfectly been illuminated. Follow-up investigations have been done by Rosenstern (1933), Hässler (1935), Bornhardt (1936), and Hering (1938) but the majority of these authors have reinvestigated their cases in the age period 16-20 years. Only in isolated cases was the age > 20 years and in no case > 23 years.

Rosenstern considers that the "Dauerform" of obesity commonly remains unchanged during development, while cases of temporary obesity, infantile obesity and puberal obesity, usually regress. He considers the latter to be especially valid in boys. The age distribution of the material is not described by the author save in connection with photographs of 6 children in various stages of development. The eldest case was 18 years while the remainder were 12—15 years at the latest examination reported. The author does not mention the development after the age of 20.

Hässler reinvestigated 28 obese children in ages 15—23. 10 cases which at hospitalization as only symptoms exhibited obesity and excessive height, at reinvestigation showed normal weight and height; 9 cases were at the follow-up still excessively tall and obese and were hypertensive. The 9 remaining cases showed at hospitalization cerebral symptoms in addition to the obesity. These cases were at reinvestigation of average height and considerable overweight.

Bornhardt reinvestigated 65 obese children (21 boys and 44 girls). The age distribution of the material at follow-up investiga-

tion is not reported but seems for at the utmost 7 of the boys to be > 19 years and for at the utmost 23 of the girls to be > 15 years. 11 of the boys and 19 of the girls attained normal weight after puberty without any treatment while 1 boy and 5 girls became normal after thyroid treatment. The author concludes that the girls remain obese more often than do the boys. The conclusion, however, is mainly based on the ages immediately prior to age 20. The author does not discuss conditions in adulthood.

Hering reinvestigated 30 patients (15 boys and 15 girls) in ages 11—23. At the follow-up examination 10 of the cases were entirely normal. 9 of these belonged to the prepuberal type of obesity and 1 case to the exogenous type. 10 giants, the majority in ages 11—15 years, were at follow-up examination tall, sturdy and overweight, but did not actually give the impression of obesity. They had high blood pressure. The obesity in 2 cases of constitutional obesity and in 3 cases of adiposogenital-like dystrophy had progressed further, and in 4 cases of cerebral obesity it had remained unchanged or had increased. Of 14 cases in which obesity was present in the parents 10 cases were still obese. Of 11 boys with disturbance of the genital development 9 had become normal, while 2 Fröhlich-like cases at the age of 15 still showed hypogenitalism.

J. Therapy.

The tendency during the development of the obese child is that the obesity at, or subsequent to, the onset of puberty spontaneously diminishes or disappears. Contributive to this is frequently the fact that the child actively begins to take an interest in his obesity and the measures taken to cure it, this as a rule previously not having been the case (Priesel & Frey 1938, Bronstein et al. 1942, and others).

Owing to the embarrassment caused the child by the obesity, physically in the form of bodily ungainliness etc., mentally because of the jibes of other children, obesity has often come to treatment. This has been instituted on different principles, all according to the conception of the origin of the obesity. The supporters of the

exogenous theory (Mulier & Topper 1934, Nixon 1934, Ellis & Tallermann 1934, Priesel & Frey 1938, Bruch 1944, and others) prescribe above all a reduction of the calories, and exercise, while the supporters of the endocrine etiology (Eidelsberg 1929/30, Dorff 1936, Gordon 1937, and others) in addition administer various kinds of hormonal treatment.

The diet has usually comprised 1 000—1 800 calories with a high-protein, low-carbohydrate and low-fat content, and a certain reduction of salt and water. The hormonal treatment has principally been carried out with thyroid hormone, but hypophyseal hormones, sex hormones and chorionic gonadotropic hormone have also been used.

Some authors stress that the treatment is not to be so severe that it is detrimental to the bodily development of the child. It is often considered sufficient for the child to "catch up" with its fat.

Treatment is usually followed by a reduction of weight or by an arrestation of weight during a continued increase of growth in height. The effect of the treatment seems, on the whole, to be satisfactory with dietary measures alone. It can not be judged whether there is a difference in the results between cases treated with diet only and those treated with diet and hormones, as the principles for treatment usually have differed in different authors. Bronstein, Halpern & Brown (1942) could in their hormone treated obesity material (46 cases) not find that hormone treatment alone, with thyroid extracts or chorionic gonadotropins had any weight reducing effect whatsoever.

In adiposogenital dystrophy-like obesity in boys it was shown by Dorff 1936, Gordon 1937, Chiari 1938, and others that the hypogenitalism, but not the distribution of the adipose tissue, frequently is amenable to hormone treatment. Shapiro (1929), however, found in his material of this type (50 cases ranging from 12—19 years) that the hypogenitalism in 48 of the cases disappeared during puberty and development without any treatment whatsoever, while the obesity only decreased but slightly.

OWN INVESTIGATION

CHAPTER II.

Obesity material and its classification.

Material.

The obesity material in the present investigation consists of cases which from 1921 to 1947, inclusive, have been hospitalized to one of the children's hospitals of Stockholm with the diagnosis of Obesity or Adiposogenital dystrophy. The majority of the cases were hospitalized for investigation of the obesity, but some were hospitalized for other reasons, the obesity therefore receiving but secondary attention.

The total number of cases with this diagnosis was 537. 33 cases were excluded from the material, the patients at the time of the follow-up investigation being dead or not to be traced, and the records being too incomplete to allow of classification of the cases.

Table 2. Follow-up examination of obesity material.

	No. of cases	Boys	Girls
Followed up. (Method)			
Examination at policlinic	230	108	122
Letter (Questionnaire)	82	40	42
Telephone contact	16	7	9
Not followed up. (Reason)	328	155	173
Brief period of observation	165	71	94
Not traced	11	7	4
	176	78	98
Total	504	233	271

The remainder of patients not followed-up: dead, not traced, uncertain diagnosis: 33 cases.

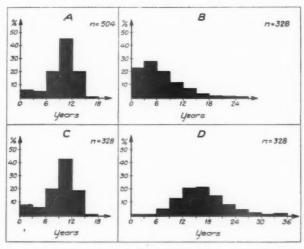


Fig. 1. Distribution of age of obesity material and number of years between hospitalization and follow-up.

A = Entire material at hospitalization (504 cases).

B = Number of years between hospitalization and follow-up.

C = Followed-up material at hospitalization (328 cases).

D = Followed-up material at follow-up examination (328 cases).

Of the remaining 504 cases 11 could not be traced (table 2), but the data recorded was sufficient to permit these cases to be included in the material. Of the remaining material a follow-up examination was done in 328 cases. Among these only 9 cases had been hospitalized less than 1 year previously. For the entire material the average time from hospitalization to the time of the follow-up investigation was 7 years. The distribution appears from fig. 1. The data in regard to the 165 cases not examined at follow-up have when necessary been supplemented by mail or telephone contacts.

The material is virtually composed of Swedish children. Only 12 are foreigners (1 Norwegian, 5 Finns, 4 Germans, 2 Italians). As the Swedish people is composed of a very pure racial stock the present obesity material is extremely homogeneous.

The distribution into different types of obesity (cf. p. 43) and different sex of the entire obesity material and the sections thereof investigated at follow-up examination is brought out in table 3. There is no difference in the age distribution for the different types of obesity (with the exception of infantile adiposity) or for the two sexes.

The follow-up examination (328 cases) was done either at a personal appearance at the hospital (230 cases) or by filling out a questionnaire (82 cases) or by telephone contact (16 cases) (table 2).

Classification.

As has clearly been seen from the review of the literature the opinions regarding the classification of the obesity are not in agreement. The greatest difficulty in classifications of this type is to ensure the utmost possible exclusion of subjective evaluations. There is especially in the "endocrine" groups such a factor of great importance. The border between the exogenous and the endogenous-constitutional types is also dependent on the evaluation of the magnitude of the "exogenous" component (luxus consumption, degree of activity). Also here the border-lines are vague.

The same uncertainty is also present in cerebral obesity. The primary disease is diagnosed as cerebral but in the literature consideration has not been taken to the change in mode of life occasioned by the disease and the subsequent effects thereof. The cerebral factor, however, is definitely established, wherefore this type should be retained as a subdivision in the classification of obesity. A certain vagueness, however, will always be inherent to the cerebral genesis of the "cerebral" obesity.

The true cases of adiposogenital dystrophy (morbus Fröhlich) with organic changes of the hypophysis or hypothalamus are rare in children. It is, however, very common for obese children without tumour to show the same typical fat distribution as in m. Fröhlich, also with external genitals which appear to be undeveloped. Small undeveloped genitals in children ought, however, not to be taken as conclusive evidence in the determination of a Fröhlich diagnosis, because of the difficulty in definitely establishing a hypogenitalism

prior to puberty. The distribution of adiposity shows all modulations over to the large group of diffuse uncharacteristic obesity. Only cases with a marked distribution of fat should therefore be diagnosed as: Fröhlich-like obesity and referred to a special group in the classification. The border-line here also is vague.

The association between "endocrine" symptoms and obesity is not established. The only definite factor is that these disturbances often occur coincidently. Children with definite "endocrine" symptoms such as menstrual disturbances, anomalies in hair growth, etc., should, however, be referred to a special group.

In infancy children physiologically are plump and chubby. Normally, this chubbiness is smoothed out during the second year of life. Children who are obese in the age 0 to 2 years are therefore described as a special type of obesity.

When these small groups of various types of obesity have been separated from the main group there remains a very large group of children, whose only "symptom" is that their weight is excessive and that they have a preponderantly diffuse noncharacteristic distribution of fat. It is these cases which in the literature are classified according to exogenous, endogenous-constitutional or endocrine groups on a more or less subjective basis. In order to avoid this, these cases should preferably be referred to a large common group.

Within this large group the exogenous factor always plays a rôle, although to a greater or lesser extent, being, according to the information available, more or less well recognized. A classification according to exogenous factors would therefore be very vague.

If there be a constitutional (endocrine?) factor, which is quite possible, this will embrace the entire group and is required for the manifestation of the obesity. The exogenous factor (luxus consumption, dislike of activity) influences the *degree* of obesity.

As two subdivisions of the main group may be classified giants ("adiposo-gigantismus") and dwarfs, the absolute stature being the only absolute factor which distinguishes them from the majority of cases in the group.

In the present child material of obesity (table 3) a further division of this large group of diffuse non-characteristic obesity (401 cases)

Table 3. Distribution of material in different types of obesity.

Type of obesity	No. of cases	Boys	Girls	No. fol- lowed up	Boys	Girls
A III	27 { 14 13	20 { 11 9	7 3	24 12	17 8	7 3
B_{II}^{II}	401 87	156 39	245 48	248 \ \begin{pmatrix} 58 \\ 190 \end{pmatrix}	98 34 64	150 24
C	52	52	0	37	37	0
D	5	0	5	5	0	5
E	19	5	14	14	3	11
Total	504	233	271	328	155	173

was done notwithstanding the introduction of an inevitably subjective factor in the investigation. An attempt was made to classify the cases according to the presence of obesity in the "family"; 0 to 1 case in one group and more than 1 case in another. As "family" are considered parents, paternal and maternal grandparents, siblings of the parents and siblings of the patient. The limit is drawn at 1 case in the "family" as 1 case occasionally may occur within a family group. There is no sharp border between the groups as the division is dependent on the subjective evaluation of the obesity in the family.

When these groups in the treatment of the material were statistically compared those cases of the group first mentioned (0—1 case of obesity) were not included in which the information as to the familiar occurrence of obesity was incomplete (20 cases).

Within the group of diffuse obesity 17 cases fall outside the limit $M\pm 2.5\,\sigma$ according to the height tables of Broman, Dahlberg & Lichtenstein. These correspond to the cases of adiposo-gigantism in the literature. Among the cases with a short stature (dwarfs) 1 case falls below $M-2.5\,\sigma$ and 6 cases fall below $M-2\,\sigma$, according to the same tables.

Obesity in *infancy* and up to the age of 2 years comprises 27 cases. These are divided into two main groups according to the occurrence of obesity in the family.

In the Fröhlich-like group have only been referred boys with a marked accumulation of fat in the sites of predeliction (52 cases).

As the distribution of fat in these cases is virtually the same as that of normal women it was considered that this type of obesity could not with certainty be diagnosed in any of the girls in the present series.

In the pluriglandular group are included 5 girls.

There are 19 cerebral cases. As "cerebral" are considered cases which are reported to have debuted in immediate association with a certain or judging by the anamnesis probable cerebral disease.

There was no case of thyrogenous obesity in the present material.

The classification of obesity in children in the present paper will be the following:

- A. Obesity at the age 0-2 years.
 - I. 0-1 case of obesity in the "family".
 - II. More than 1 case of obesity in the "family".
- B. Diffuse non-characteristic obesity.
 - I. 0-1 case of obesity in the "family".
 - II. More than 1 case of obesity in the "family".
- C. Fröhlich-like obesity (Adiposogenital-like dystrophy).
- D. Pluriglandular obesity.
- E. Cerebral obesity.

It is again emphasized that these groups of obesity merely designate certain main types and that between these main types there occurs every intermediate type and every combination imaginable.

Statistical methods.

The following statistical methods have been used in the statistical computations.

The standard deviation (σ) was computed according to the formula:

$$\sigma = \pm \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$$

where x is a variate, \bar{x} the mean and n the number of observations.

The standard error of the mean (εM) was obtained by the formula:

$$\varepsilon(M) = \pm \frac{\sigma}{\sqrt{n}}$$

The standard error of a frequency expressed in per cent (εp) was computed according to the formula:

$$\varepsilon(p) = \pm \sqrt{\frac{p(100-p)}{n}}$$

where p is the percentage and n the number of observations.

The standard error of a difference (εD) between two means or two percentages was obtained by the formula:

$$\varepsilon$$
 (D) = $\pm \sqrt{\varepsilon_1^2 + \varepsilon_2^2}$

where ε_1 and ε_2 denote the standard error of the means or percentages in question.

A difference has been denoted as statistically *probable* when between 2 to 2.6 times its standard error corresponding to a probability for coincidence (P) of 0.05—0.01, *very probable* when between 2.6 to 3.3 times its standard error (P = 0.01 - 0.001), and *significant* when exceeding 3.3 times its standard error (P = < 0.001).

The regression and correlation computations were performed according to R. A. Fisher (cit. Bonnier & Tedin 1940).

CHAPTER III.

Heredity.

Material.

In the present obesity material there are in many instances height and weight records for one or both parents. In order to obtain a correct assessment of the occurrence of obesity among the parents of the obese children weight and height reports were obtained also for the parents of 200 normal children from various social groups (100 boys and 100 girls). The children were pupils from an Elementary School of Stockholm and in the ages 6 to 15 years with a Rohrer-index within \pm 2 σ according to the Rohrer-index table of Broman, Dahlberg & Lichtenstein. The age distribution of both groups of parents was similar.

In the obesity material were included cases of diffuse obesity (Type B), Fröhlich-like obesity (Type C) and cerebral obesity (Type E), cf. p. 43. This material was treated both as one large group and also divided into two equally large groups, one more obese and one less obese group ,with the median ($+3.5\,\sigma$ according to the Rohrer-index table) as limit.

Results.

On treatment of the normal material and the obesity material both sexes as well as different types of obesity gave entirely conformant results. The combined result is shown in table 4.

It appears from the table that the average Rohrer-index value of the normal children is 1.19 which is in approximate agreement with the values given in the normal standard for the comparable age period.

A comparison between the Rohrer-index values for the parents of normal and of obese children reveals a significant difference

Table 4. Rohrer-index for normal and obese children and their parents.

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Normal and obese children	n	σ	$M \pm \varepsilon (M)$	$D \pm \varepsilon(D)$	
	Children				
Normal	200 478	$0.10 \\ 0.28$	$ \begin{vmatrix} 1.19 \pm 0.01 \\ 1.70 \pm 0.01 \end{vmatrix} $	$+0.51 \pm 0.0$	
Less obese	239 239	$0.23 \\ 0.24$	$\begin{array}{c} 1.55 \pm 0.02 \\ 1.84 \pm 0.02 \end{array}$	$+0.29 \pm 0.0$	
		F	ather		
Normal	$\frac{200}{282}$	$0.18 \\ 0.20$	$1.40 \pm 0.01 1.47 \pm 0.01$	$+0.07\pm0.0$	
Less obese	144 138	$0.19 \\ 0.22$	1.45 ± 0.02 1.48 ± 0.02	$+0.03\pm0.0$	
		M	lother		
Normal	200 304	$0.22 \\ 0.27$	$egin{array}{c} 1.48 \pm 0.02 \ 1.63 \pm 0.02 \ \end{array}$	$+0.15\pm0.0$	
Less obese	160 144	$0.25 \\ 0.28$	$ \begin{vmatrix} 1.58 \pm 0.02 \\ 1.69 \pm 0.02 \end{vmatrix} $		
		Father	and mother		
Normal	400 540	$0.20 \\ 0.26$	$\begin{array}{ c c } 1.44 \pm 0.01 \\ 1.54 \pm 0.01 \end{array}$	$+0.10\pm0.0$	
Less obese	276 264	0.22 0.27	1.50 ± 0.01 1.58 ± 0.02	$+0.08 \pm 0.0$	

n =number of cases.

 $M \pm \varepsilon (M) = \text{mean} \pm \text{standard error of the mean.}$

 $D \pm \varepsilon (D) = \text{difference} \pm \text{standard error of the difference.}$

The median of the obesity material lies at $+3.5\,\sigma$ according to Broman, Dahlberg & Lichtenstein's Rohrer-index table.

Less obese children = Rohrer-index $< + 3.5 \sigma$.

More obese children = Rohrer-index $< + 3.5 \sigma$.

between the two groups in the fathers as well as the mothers. The difference is twice as great in the mothers as in the fathers. This shows that obesity is more common among the mothers of the obese children. This result confirms the reports in the literature with regard to the female predisposition for obesity.

When the Rohrer-index values of the parents of more and of less obese children, respectively, are compared, the same relations are obtained as in the comparison between the normal mate-

Table 5. Percentual occurrence of obesity among parents of obese individuals.

Authors	No. of cases	Neither obese	Obese	Both	
			father	mother	obese
Bauer 1929	?	17	18	42	23
Gurney_1936	75 adults	17	15	43	25
Mossberg 1948	270 children	20	12	36	32

The values originally reported by Bauer only refer to that portion of the material in which either of the parents was obese. The values are here corrected to include the entire material.

rial and the entire obesity material. The differences, however, are smaller, especially in regard to the fathers.

In cases where Rohrer-index values for *both* of the parents in the material are available the same comparison has been done. The result is the same as that related above (cf. table 4).

The percentual distribution of the Rohrer-index values of both parents around the respective mean values has been determined. The parents of both the normal and the obese children hereby show a negative skewness in the distribution. The skewness is most pronounced in the latter.

The obesity material has further more been computed according to the subjective interpretation offered with regard to the occurrence of obesity among the parents. The percentual distribution has been determined. On comparison between the parents of less obese and more obese children the results are on the whole in agreement with those described above. The differences between the groups, however, are statistically less significant. Here also the mothers show the greatest difference with a statistically very probable difference, + 13.8 \pm 5.2 %.

The subjective interpretation of obesity among the parents in those cases in which index reports are available for father and mother of the obesity material has in table 5 been compared with the correspondent reports of BAUER and GURNEY. There is good conformity between the results.

It has in the field of genetics been shown that certain factors

are hereditary and essentially necessary for the individual's power to live and to develop in a definite direction, while other factors are less essential and exert a more or less uniform extrinsic influence (Muller 1947). To the former class belongs the predisposition towards obesity, to the latter belongs the exogenous element of obesity (luxus consumption, indolence).

The results described above are thus due to two factors, endogenous and exogenous, which it is not possible to segregate. It has not been possible to determine to which extent the obesity has been constitutionally endogenous and to which extent it has been exogenous. The course of the heredity can in this material not be traced.

Summary of the heredity in obesity.

The investigation shows that obese children have obese parents more frequently than do normal children and that the higher the degree of the obesity in the children, the more frequently have the parents, and particularly the mothers, a higher degree of obesity also.

CHAPTER IV.

Physical and mental development.

Age at the onset of obesity.

In 493 cases information has been received regarding the age at the onset of obesity. It appears from the diagram (fig. 2) that there are two peaks and that these occur at approximately the same ages as those described in the literature.

In 247 of the cases the statement was "always obese". This specification of time must be more or less erroneous because of the disproportionate size of the group, and is perhaps mainly due to poor memory on the side of the parents. The best interpretation

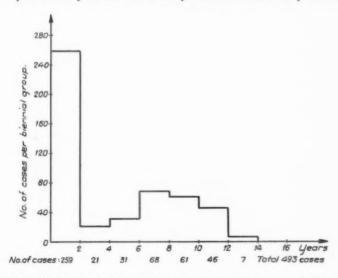


Fig. 2. Distribution of obesity material acc. to the age at onset of obesity.

Table 6. Age at debut of obesity. Percentual distribution in different age groups.

Authors	No. of cases	0-4	56	7—9	10—11	12—14	> 14 years
Rony (1932)	50	64	8	10	16	0	2
Ellis &Tallermann (1934)	50	26	14	32	22	6	()
Gordon (1937)	50	30	?	?	?	?	?
Mossberg (1948)	493	57	6	22	11	4	0
	boys 228 girls 265	51 62	8 5	24 20	12 10	5 3	0
		0—8	> 8 years				
Bruch (1939)	83	82	18				
	boys 45 girls 38	75 89	25 11				
Mossberg (1948)	493	77	23				
	boys 228 girls 265	73 80	27 20				

of this unsatisfactory specification of time would probably be that the patient has become obese during one of the first 3 years of life.

It appears from table 6 that the values obtained are best in agreement with Rony's material of 1932. If the values prior to the age of 8 are combined in a group comparable with Bruch's group, there is good accordance with her material also.

The age for the onset of obesity shows the same peaks in different main types of obesity. There is no statistically significant sex-linked difference.

The two large subdivisions of the diffuse obesity (Type B, cf. p. 43) exhibit a difference in frequency of the age at onset of obesity before and after 6 years of age. Cases with >1 obese individual in the family (Type B II) become obese before 6 years of age in a greater frequency than cases with 0-1 obese individual in the family (Type B I). When the obesity debuts after the age of 6 the reverse is the case. For the age groups 0-3 and 8-9 years the difference is statistically significant.

In cases with 0 to 1 obese relative (Type B I) the debut of obesity

(1

Table 7. Frequency in % of more obese children in various types of obesity in relation to age at the onset of obesity (< or ≥ 6 years).

		More obese children			
Obese at age	n	Frequency in %	$D \pm \varepsilon (D)$		
		Obesity type B	B I.		
< 6 yr ≥ 6 yr	23 42	$\begin{array}{c} 47.8 \pm 10.4 \\ 21.4 \pm 6.3 \end{array}$	-26.4 ± 12.2		
		Obesity type B	II.		
< 6 yr $\ge 6 \text{ yr}$	200 100	$57.9 \pm 3.5 \ 39.0 \pm 4.9$	$\left ight. ight18.9 \pm 6.0$		
		Obesity type	C.		
< 6 yr ≥ 6 yr	28 22	$\begin{array}{c} 71.4 \pm 8.5 \\ 36.3 \pm 10.2 \end{array}$	-35.1 ± 13.3		

n = number of cases.

 $D \pm \varepsilon$ (D) = difference \pm standard error of the difference.

Classification of obesity in types cf. p. 43.

occurs at 0 to 3 years in 30.8 \pm 5.7 % (20/65), while in the group with several obese relatives (Type B II) obesity debuts at 0 to 3 years in 59.0 \pm 2.8 % (177/300) of the cases. The difference 28.2 \pm \pm 6.4 % is statistically significant.

In the age group 8 to 9 years the children with obesity of Type B I show a frequency for the onset of obesity of 29.3 ± 5.6 % (19/65) the figures for the other large subdivision (Type B II) being 9.7 ± 1.7 % (29/300). The difference 19.6 ± 5.9 % is statistically significant. In the other age groups the differences are not even statistically probable.

When the obesity material expressed in Rohrer's index is distributed in a more obese and in a less obese group with the median $(+3.5\,\sigma)$ as limit and is placed in relation to the age at the onset of obesity there is a definite difference in the distribution of the cases within the both groups. The obesity material of different types, in which obesity has debuted prior to age 6 belong approximately twice as often to the *more* obese group compared with those cases in which the obesity has debuted subsequent to age 6 (table 7). The difference between the values ranges statistically between probable and significant. There is no sex-linked difference.

Initiating causes of obesity.

The presence of a coincidence between disease (cerebral, non-cerebral) and the onset of obesity has been investigated. Information pertinent to this was in several cases verified by previous determinations of weight and height. Initiating cerebral diseases were (number of cases in brackets): hemorrhage at birth (9), cerebrocele with hydrocephalus (1), commotio cerebri (1), meningitis (2), morbilli with symptoms of encephalitis (6). Total 19 cases.

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Immediately preceding non-cerebral diseases may be divided into 4 large groups: those requiring sanatorium treatment or feeding-up cures (7); infectious diseases (18); operations (14); group with various diseases (5). Total 44 cases.

The sanatorium and feeding-up cures include children with tuberculosis (5), astma (1), and general somatic debility (1); the infectious group: otitis (3), angina tonsillaris (1), bronchitis-pneumonia-pleuritis (4), rheumatic infection (2), scarlatina (2), pertussis (1), morbilli without symptoms of encephalitis (3), rubeola (1), varicelle (1); the operation group: vaccination for small-pox (3), tonsillectomy and abrasio (9), appendectomy (2); various diseases: fractures (3), brachialgia (1), nephrolithiasis (1).

If from the entire material are excluded those cases which "always" have been obese, cases of cerebral obesity and such cases in which there are no data in regard to the onset of obesity, it appears that obesity has debuted in immediate association with disease in 44 out of 233 cases, thus 18.9 %. There is no significant difference in the occurrence in different types of obesity nor is there a sex-linked difference (Type B I 23 % (11/47), Type B II 18 % (25/141), Type C 13 % (4/32)).

In all of these cases the disease involves a change in the mode of life usually involving bed-rest. The diseases are in many cases protracted and, except for the initial phase, often without serious deterioration of the child's general condition. The conditions are thus favorable for the arisal of a disproportion between the nutriment ingested and that utilized.

Weight at birth.

For comparison with the normal weight at birth of Swedish children the values of v. Sydow (1940) were used.

The different types of the obesity material all — and especially the cases of gigantism — exhibit a tendency towards high weight at birth. The weight at birth of the entire material are recorded in table 8. Both of the sexes show a statistically significant difference for birth weights $> 4\,000$ gm.

The relation between the weight at birth and age at onset of obesity shows a tendency towards higher weights at birth in cases with an early (prior to 6 years) onset of obesity $(28.7 \pm 2.7 \% (78/272))$ as against $21.7 \pm 3.4 \%$ (33/152)), but the difference $7.0 \pm 4.3 \%$ is not even statistically probable.

Height and weight. Rohrer's index.

The distribution of the *height* of the obesity material is represented in fig. 3. The cases in infants have not been included, as the height tables of Broman, Dahlberg & Lichtenstein do not include ages

Table 3. Weight at birth of normal and obese children. Normal values acc. to v. Sydow (1940).

		Boys		Girls				
	n	$M \pm \varepsilon(M)$	$D \pm \varepsilon(D)$	n	$M \pm \varepsilon(M)$	$D \pm \varepsilon(D)$		
		W	eight at birth	'≤ 2	2 500 gm.			
Normal Obese	522 204	$\left \begin{array}{c} 4.8 \pm 0.9 \\ 4.4 \pm 1.4 \end{array}\right $	-0.4 ± 1.7	$\frac{551}{229}$	$igg egin{array}{c} 6.5 \pm 1.1 \\ 6.1 \pm 1.6 \\ \end{array} igg $	— 0.4 ± 2.0		
		Wei	ght at birth 2	510-	-4 000 gm.			
Normal Obese	$\begin{array}{c} 522 \\ 204 \end{array}$	$\begin{vmatrix} 79.3 \pm 1.8 \\ 69.1 \pm 3.2 \end{vmatrix}$	-10.2 ± 3.7	$\frac{551}{229}$	$egin{array}{ } 86.4 \pm 1.5 \\ 68.6 \pm 3.1 \\ \hline \end{array}$	-17.8 ± 3.4		
		V	Veight at birth	> 4	000 gm.			
Normal Obese	522 204	$ 15.9 \pm 1.6 \ 26.5 \pm 3.1 $	$+10.6 \pm 3.5$	551 229	$egin{array}{c c} 7.1 \pm 1.1 \ 25.3 \pm 2.8 \ \hline \end{array}$	$+18.2 \pm 3.0$		

n = number of cases.

 $M \pm \varepsilon(M) = \text{mean} \pm \text{standard error of the mean.}$

 $D \pm \varepsilon (D) = \text{difference} \pm \text{standard error of the difference}.$

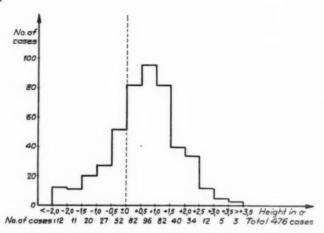


Fig. 3.Height distribution of the material of obese children expressed in multiples of the normal standard deviation (σ) acc. to Broman, Dahlberg & Lichtenstein's height tables.

----- Denotes the average height of normal children acc. to Broman, Dahlberg & Lichtenstein's height tables.

below 1 year. In some cases data in regard to height were lacking in the records. The number of cases included in the curve of frequency is 476. 74.4 % of these lie above the normal average value for the age and the peak of the frequency curve lies at + 0.5–1.0 σ . There is no sex-linked difference nor difference between different types of obesity.

The weight of the obesity cases is in 474 cases assessed in relation to the height according to Broman, Dahlberg & Lichtenstein's height-weight-tables. According to these tables the weight exceeds + 2 σ in 85.2 % of the cases and in 56.5 % it exceeds + 3 σ . The distribution shows a skewness in the direction of large values (fig. 4). The heaviest children have an excess weight which expressed in σ lies above + 10. In 2 cases of slender build and a low degree of obesity the weight is even below the average for normal children.

In all types of obesity there are throughout more boys than girls with overweights exceeding + 5 σ : boys 21.7 \pm 2.8 % (46/212); girls 16.4 \pm 2.3 % (43/262). The difference 5.3 \pm 3.6 % is not

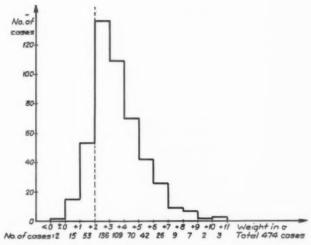


Fig. 4. Weight distribution of the material of obese children expressed in multiples of the normal standard deviation (σ) acc. to Broman, Dahlberg & Lichtenstein's height-weight tables.

----- Denotes the border $M+2\,\sigma$ acc. to Broman, Dahlberg & Lichtenstein's height-weight tables.

even statistically probable. In lower degrees of obesity the opposite conditions are found. This circumstance suggests a certain correlation with the statement in the literature that males attain the highest degrees of obesity.

The material has also been computed according to *Rohrer's index*. The curve of frequency expressed in σ shows a peak between + 3 σ and + 4 σ . The median lies at + 3.5 σ . The case distribution is the same as that of the weight curve.

When the obesity material is divided, according to Rohrer's index, into a more obese group and a less obese group with the median (\pm 3.5 σ) as limit, one finds for the large group of diffuse non-characteristic obesity, Type B, a significant difference in the distribution of the cases between the two subdivisions of the group, B I and B II (0–1 and > 1, respectively, obese individual in the family, cf. p. 43). In the group "more obese" children are included 29.9 \pm 5.6 % of the 67 cases of Type B I with complete

reports of obesity in the family and 52.6 \pm 2.8 % of the 310 cases of Type B II, in which it has been possible to determine Rohrer's index. The difference between these percentual figures, 22.7 \pm 6.3 % is statistically significant. There is no sex-linked difference. The result seems to show that those cases in which obesity occurs in > 1 case in the family more frequently become more obese than those cases in which obesity is present in \leq 1 case in the family.

The 52 cases of Fröhlich-like obesity, Type C, are about equally distributed in the more and in the less obese group of children (53.8 % and 46.2 %), respectively).

Development of puberty.

The development of puberty has been studied according to the same lines as those of Bruch 1941 (cf. p. 19), in spite of the subjective factor involved hereby. The development of the breasts (girls), the genitals (boys) and the distribution of pubic and axillary hair has at each examination been recorded as one observation in the tables (tables 9 and 10). 1 or 2 observations have been done on each patient (hospitalization and follow-up examination). Data in the records have only been accepted when a specified description has been recorded. General remarks such as "beginning puberal development" have not been accepted. The tables include all the cases of obesity, with the exception of the Fröhlich-like cases, pluriglandular cases, and 1 case of cerebral obesity with general marked mental retardation.

The values for normal children given by Bruch can not be used as they are not based on a Swedish material. The menarcheal age in Sweden has been analyzed in an exhaustive study by Lennér (1944). With regard to the urban population, which corresponds with the nature of the obesity material, the average menarcheal age of 1 143 Swedish girls was reported as 14.397 years ($\sigma=\pm 1.567$ years). In the youngest cases, which best correspond to the age distribution of the obese children the menarcheal age was barely 14 years.

The distribution of the menarcheal age of the obesity material is presented in table 9. The average value is seen to be 13 years,

Table 9. Puberal development in girls.

Age in years	Total No. of observa- tions	No signs of puberty	Begin- ning develop- ment	Advanced develop- ment	Post- puberty	Menarche
< 8	34	33	1	_	_	_
8 9	17	16	1	_		
9-10	22	14	7	1		_
10-11	29	17	12			4
11-12	34	12	16	6	-	20
12-13	28	4	12	10	2	34
13-14	19	_	3	12	-1	31
14-15	11		1	4	6	25
15-16	17	_	1	3	13	5
≥ 16	49				49	1
	260					120

thus about 1 year earlier than the age normal for Swedish girls. This is in agreement with Bruch's results.

It also appears from the tables that there is good agreement between the successive development of the secondary sexual characteristics and the menarcheal age. In cases of "advanced development" the distribution of the cases in different ages is identical with the distribution of the menarcheal age.

It is not possible to compare the boys of the obesity material with normal Swedish boys as there, as far as known, is no normal Swedish material published. A classification is done in analogy with Bruch's investigation and the case distribution of that group which shows increased growth of the genitals and growth of the pubic hair is studied. The peak was at the age group 13 to 14 (table 10); in comparison with the group of girls with beginning puberal development it was approximately 2 years later than the girls. This is the same relationship as that found by Bruch in correspondent groups of her material.

In view of the reports in the literature it is of particular interest to study the puberal development of the Fröhlich-like cases. The number of cases observed is too small to allow of any definite opinions (10 observations in the group with commencing genital development and growth of pubic hair), but the cases are distributed along the same lines as the great majority of the obesity

Table 10. Puberal development in boys.

Age in years	Total No. of observa- tions	No signs of puberty	Begin- ning growth of genitals	Pubic hair	Axillary hair, etc.	Post- puberty
< 9	56	56	_		_	_
9-10	12	11	1	_	-	_
10-11	22	17	4	1		-
11-12	24	17	3	4	_	_
12-13	19	9	6	3	1	-
13-14	20	1	5	12	2	
14-15	9	_	1	3	5	_
15-16	14	_	_	1	8	5
16-17	1	_		-	1	_
≥ 17	32	_	_			32
	209					

cases. There does not, however, appear to be any late puberal development.

As puberty in normal boys on an average is considered to occur a couple of years later than in normal girls it can be established that *puberty in obese boys* is not retarded but that it probably on an average has the same early onset as in obese girls.

According to the literature on the normal increase of growth of American children it appears that the acceleration of growth sets in at 2 to $2\frac{1}{2}$ years prior to menarche (Swedish children $2\frac{1}{2}$ to 3 years); that growth is entirely terminated 4 to 5 years subsequent to menarche; that cases with an early menarche have the greatest annual increment of growth 1 year prior to menarche and that cases with late menarche have the greatest annual increment of growth 2 years prior to menarche; that cases with early menarcheal age have a greater yearly increment of growth than cases with a late menarcheal age; that cases with the greatest acceleration of growth during puberty attain a lesser absolute height than cases with a lesser yearly increment of height.

In 27 of those cases of the obesity material whose menarcheal age was known there are frequent reports on the development of height. These cases are divided into 2 groups according to the menarcheal age: an early group with menarche at 10 to 13 years (19 cases), and a late group with menarche at 13 to 16 years (8

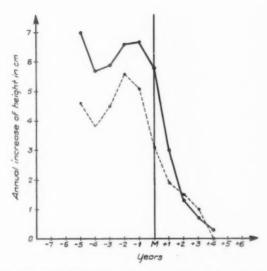


Fig. 5. Average annual increase of height at early and late menarche of obese children.

M = menarcheal year.

menarche at 10—13 years (19 cases).

menarche at 13—16 years (8 cases).

The diagram shows that obese children have a distinct acceleration of growth already 3 to 4 years prior to menarche which is clearly earlier than that in normal children.

cases). The results are reported in fig. 5. The obese children show a distinct acceleration of growth already 3 to 4 years prior to menarche, a condition clearly divergent from that in normal children. In other respects the curves show conditions similar to those in normal children.

Obesity cases aged 18 or more at the follow-up examination were grouped in 2 menarcheal groups of 10 to 13 years and 13 to 16 years, and compared with consideration to absolute height. No statistical difference is demonstrable in this small material (47 cases).

Different menarcheal ages in relation to the age at the onset of obesity do not show any definite correlation in this obesity material. The cases with early as well as with late menarcheal age become, in the majority of the cases, obese at 0 to 6 years of age.

Development of intelligence.

The mental development of the obese children has in this material not been subject to a thorough analysis. It is, however, evident that a problem of this nature often is present and would well be worthy of future study.

In this analysis the development of intelligence has been investigated in a number of cases. As different methods were followed by the various investigators, however, the value of a grouping of the entire material is but negligible. Accordingly, only those 52 cases (3 to 14 years of age) are included which were tested according to *Terman-Merrill's method* (ALICE HELLSTRÖM'S Swedish adaptation) and where the investigator was specialized in intelligence tests. Cases of birth trauma with mental retardation are not included.

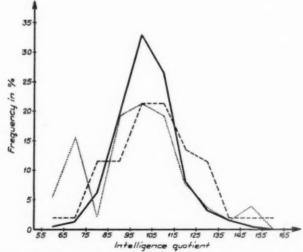


Fig. 6. Development of intelligence of obese children acc. to Terman-Merrill.

Normal Swedish children, 6—12¹/₂ yr (336 cases).
Intelligence age of obese children versus chronologic age, 3—14 yr (52 cases).

The intelligence age is in advance of the chronologic age but in agreement with the height age.

The results, irrespective of sex, show an advanced mental development in relation to chronologic age (fig. 6). The comparison was done against an average material of Swedish school-children in the ages 6 to $12\frac{1}{2}$ years (A. Hellström).

As obese children are taller than the normal average their intelligence age is also compared with the age correspondent to their height (height age). Here the curve of distribution for high grades of intelligence closely follows the normal curve. In lower grades of intelligence the curve shows a marked peak.

The 3 Fröhlich-like cases included exhibit in relation to their chronologic age a normal or advanced mental development (2+1); in relation to their height age their mental development is normal or retarded (2+1), thus apparently showing the same tendency as the entire obesity material.

The obesity material thus appears to consist of bodily advanced children, whose mental development generally is on a par with the height development, only in exceptional cases being retarded in comparison with the physical development.

Summary of the development of obese children.

The physical and mental development of the majority of the obese children exhibits a definite acceleration demonstrated already by the tendency towards a heavy weight at birth. During the development of the obese children cases with > 1 obese individual in the family are more frequently more obese than cases with 0-1 case of obesity in the family. The former cases also more frequently become obese at an earlier age than the latter. During the development of the child the average stature will exceed that normal for the various ages. An expression for this increased intensity of development is in the case of the girls partly the onset of puberal acceleration of growth, early in comparison with that of the normal material (4 years prior to menarche) and, partly, the earlier development of puberty (menarcheal age at 13). In principle, no difference between boys and girls is demonstrable. In obese children the "Periode der zweite Fülle" or an eventual so-called "pre-puberal" obesity may therefore on the average be stated to commence at 9 years of age (6 to 12 years). In agreement with this there is in these ages a second peak for the debut of obesity. The mental development also in the majority of the cases shows an acceleration suggesting a close association between somatic and mental development. The factor stimulating growth seems to exercise a general influence.

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CHAPTER V.

Basal metabolism.

Material.

Basal metabolism determinations were in the present material carried out on 138 boys and on 181 girls. The children's ages ranged from 4 to 15 years. On these children 149 and 196, respectively, BMB determinations were made, each comprising at least 2 determinations. Untreated cases of diffuse obesity (Type B) and cerebral obesity (Type E), cf. p. 43, were first computed separately and then as a larger group. Untreated Fröhlich-like cases (Type C) and cases which at the time of the BMB determination were receiving treatment with thyroid or gonadotropic hormone were computed separately.

Methodics.

All of the BMB determinations were made on hospitalized children. The children were not fed since the previous evening and were on the morning of the test (approx. 7 o'clock) brought recumbent to the laboratory. Here they were rested in absolute quiet at least 30 minutes prior to the investigation. Krogh's apparatus was used and the children were awake during the test. Two five-minutes observations of the 0_2 -consumption were made and the average of these was used as a basis for the computations. The determinations were repeated on the following day and sometimes on several days running. By using the mean of 2 determinations made on successive days there was a greater certainty of obtaining a correct representation of the true basal metabolism of the subject.

The caloric consumption found was then referred to the Lewis et al. standards per hour referred to weight, to height and to total surface area, and for calories per hour per square meter referred to age. Broman, Dahlberg & Lichtenstein's weight, height and Rohrer-index tables with the coefficients of variation there defined were used. The surface area was determined by the method reported by Lewis et al. according to the Du Bois height-weight formula with the aid of the nomogram of Boothby & Sandiford (1920).

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Results.

In order to establish the potential influence of the *training* on the BMB values the two first values obtained in the present material were compared. In 68 per cent the first value was the greatest,

At the first BMB determination the children often showed a marked uneasiness and apprehension, factors which increase the metabolism. This psychic factor should not be present in a "basal" state. Accordingly, if by training is understood an elimination of psychic factors and a "basal" state for excitable children thereby is attained, the training in a number of cases has a certain effect.

Further, the regimen of the hospital (no snacks in the pantry, no eating between meals, less sweets etc.) and the unfamiliar surroundings often cause a decrease in the exogenous factors. This implies a decrease in the caloric intake. Several authors, Benedict et al. (1919), Helmreich (1927), Johnston & Maroney (1936) have shown that the BMB value under such circumstances gradually slopes towards a new level.

Both of these factors, the psychic as well as the exogenous, so influence the BMB values found that a higher initial value frequently is obtained. As was mentioned above a higher initial value is more frequent in the present investigation also.

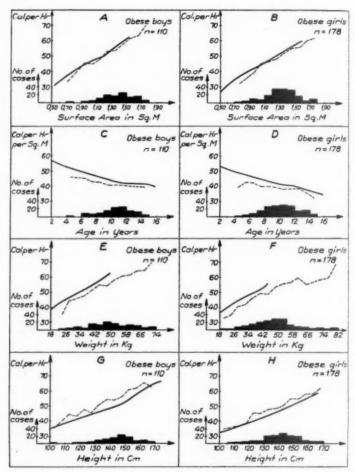
Cases of diffuse obesity and cerebral obesity (110 determinations on boys and 178 on girls) showed in 75 per cent of the cases a maximum difference of 5 per cent between the two BMB values. Computations were done separately for the differences ≤ 5 per cent and > 5 per cent. No differences between the means were demonstrable in BMB values obtained in different hospitals, between the values of boys and of girls, between the values of different types of obesity, nor in the distribution of the values within the two groups. The material is therefore in the sequel treated as a single large group.

Referred to the various Lewis standards it appears that the values for obese children of this material are in very close agreement with the standard for the total surface area. They show, however, a trend towards rather low mean values (fig. 7 A—B). Referred to the standard for calories per hour per square meter the mean values are definitely lower (fig. 7 C—D), being lowest with reference to the weight standard (fig. 7 E—F). With regards to height the values of the present material are clearly higher than those of the Lewis height standard (fig. 7 G—H).

The values are in a scatter diagram compared with the surface area standard of Lewis et al. Their distribution is in good agreement with the normal dispersion. There is here also, however, a trend towards somewhat lower values (fig. 8 and 9). The deviation of the normal BMB values \pm 18 % (correspondent to $M\pm3$ σ) is thus apparently valid for obese children also.

If the total BMB values of the obese children are compared with that of normal children of the same ages the values of the obese children are manifestly higher. Obese children, however, have a height which on the average exceeds that of normal children of comparable ages (cf. fig. 3 p. 54). If therefore the BMB values are referred to the height age instead of to the chronologic age a value approximately 5 calories per hour higher than that of normal children will be obtained. This shows that the total basal metabolism of the obese children is greater than that of normal children of the same height and sex.

The onset of *puberty* of obese children is earlier than the normal occurring in boys at approximately 10 to 14 years (table 10, p. 58) and in girls at approximately 9 to 13 years (table 9 p. 57). It appears from the diagram for calories per hour per square meter referred to age (fig. 7 C, D) how during the puberty the annual decrease lessens. In girls the change seems to occur at the age of 8 to 9 years, which is 4 to 5 years prior to their average menarcheal age. This age corresponds to the period of the onset of the prepuberal acceleration of growth (fig. 5 p. 59). In boys the correspondent change seems to occur at the age of 10 to 11, which is in good agreement with the later puberal development of the obese boys compared with the obese girls.



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Fig. 7. Average BMB values for 110 obese boys and 178 obese girls referred to the Lewis et al. normal standards expressed in calories per hour referred to total surface area (A—B), weight (E—F), height (G—H), and for calories per hour per square meter referred to age (C—D).

Lewis et al. standards.
.... Means of obese children.

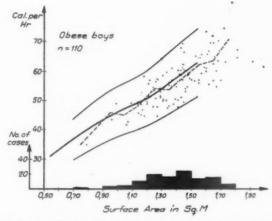


Fig. 8. BMB values for 110 obese boys expressed in calories per hour referred to total surface area and their mean values (broken line), and the Lewis et al. normal standard for total surface area with the ranges of variation $\pm 3\sigma = \pm 18\%$ (unbroken lines).

The diagram depicts the trend in obese boys towards rather low mean values referred to the Lewis standard, while the scatter is in good agreement with the normal (\pm 18 %).

The condition in normal children, that the decrease in caloric metabolism (expressed in calories per hour per square meter) lessens during puberty is thus valid for obese children also. The diminution of the decrease appears to begin earlier than in normal children and coincident with the onset of the puberty and the prepuberal growth acceleration of the obese children.

It is in obesity of essential importance to demonstrate the influence of the overweight on the BMB value. The material has therefore been grouped in various degrees of overweight and the basal metabolism has been referred to the 4 different Lewis standards (fig. 10). The number of cases varies, as the body proportions of the obese children in many cases exceed the maximum and minimum values included in the Lewis standards. Overweight is expressed in multiples of the normal distribution (σ) in different ages according to Broman, Dahlberg & Lichtenstein's Rohrer-index table. It appears from the diagram that increasing overweight

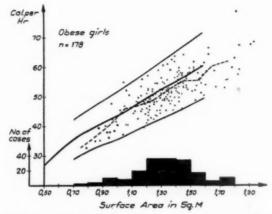


Fig. 9. BMB values for 178 obese girls expressed in calories per hour referred to total surface area and their mean values (broken line), and the Lewis et al. normal standard for total surface area with the ranges of variation $\pm\,3\,\sigma=$ = $\pm\,18$ % (unbroken lines).

The diagram depicts the trend in obese girls towards rather low mean values referred to the Lewis standard, while the scatter is in good agreement with the normal $(\pm 18 \%)$.

referred to the height standard obviously gives increasing BMB values (+ $1.1 \% \rightarrow + 13.4 \%$), while they referred to the other standards give values of the same magnitude regardless of the degree of obesity. Referred to the standards for the total surface area the values are in closest agreement with the ideal (— $5.3 \% \rightarrow -2.1 \%$) with reference to the standards per square meter body surface they are somewhat lower (— $7.7 \% \rightarrow -5.8 \%$), being lowest with reference to the weight standards (— $9.3 \% \rightarrow -10.6 \%$). It thus appears that reference to the Lewis standard for the total surface area regardless of the degree of overweight, gives the values most closely approaching the ideal and that this standard seems to be that most appropriate for these obese children.

The increase of surface area and body weight in obesity thus seems to be in good correlation with the increase in total metabolism. The trend of the values to fall below the standard may possibly be due to the fact that the Lewis standards are based on

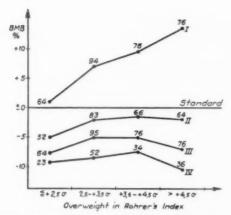


Fig. 10. Average percentual BMB values for obese children with various degree of overweight. BMB values referred to the normal standards of Lewis et al. (I—IV). Overweight expressed in multiples of the normal standard deviation (σ) in various ages according to Broman, Dahlberg & Lichtenstein's Rohrerindex table.

I = Calories per hour in relation to height.

II = Calories per hour in relation to total surface area.

III = Calories per hour per square meter surface area in relation to age.

IV = Calories per hour in relation to weight.

· The numerals show the number of cases.

The diagram depicts the marked increase of the BMB values referred to the height standard at increasing overweight, while they referred to the other standards give values of the same magnitude.

values obtained by determinations on outpatients, the child having been in motion prior to the determination; that different apparatus were used; that the weight and height values of the obese children frequently exceed the maximum and minimum values reported in the Lewis standards; or, that the obese children have more inactive tissue than the normal children. The parallelism of the values seems, however, to indicate that the conditions by and large are similar.

When the obesity cases are separated into a more obese and a less obese group with the Rohrer-index $+3.5\,\sigma$ as border-line, a statistically significant difference is obtained only with reference to the height standard. The mean values are $+4.6\,\%$ and $+11.4\,\%$,

respectively, and the difference is 6.8 \pm 1.2 %; the correspondent values with reference to the total surface area standard are — 3.3 % and — 1.8 %, respectively. The difference 1.5 \pm 1.1 % is of no importance.

The height of the various overweight groups in fig. 10 is on an average uniform. The great increase of the BMB values at increasing overweight in their relationship to the height standards must then imply that the additional tissue (fat, muscles, etc.) is metabolistically "active".

Twenty-seven of the children have been obese less than 1 year. It may be supposed that the overweight in these cases probably is due to a proportionally greater amount of fatty tissue as the musculature is probably not as yet developed to carry the fat. The average BMB values in various degrees of overweight show in these cases referred to the height standard (\pm 0 \rightarrow + 11.2 %) and to the weight standard (- 8.0 \rightarrow - 9.6 %) no deviations from the values for the entire material (cf. p. 68). The result shows that the adipose tissue probably has a heat producing capacity. If the fatty tissue were "inactive" the BMB values for these cases would at the greatest overweights have shown but a moderate increase in relation to the height standard and a definite decrease in relation to the weight standard. The concept of the adipose tissue as not being "inactive" tissue but participating in the metabolism of the body thus seems to be correct.

The cases of gigantism (11 BMB determinations) and dwarfism (7 BMB determinations) included in Type B show on comparison with the Lewis standards for the total surface area a trend towards low BMB values. All but one of the values fall within the normal limits of dispersion, as far as these latter are indicated. The relations to the other Lewis standards show similar conditions. For giants with an overweight not exceeding $+2.5\,\sigma$ according to the Rohrer-index tables and also for dwarfs a reference to the height standard perhaps is best in agreement. The relation to the degree of overweight does not show anything which deviates from the conditions described above.

If it from these few cases be permissible to draw a conclusion it may be established that in cases with such extreme body proportions

as those of giants and dwarfs for whom the standards are not intended, the BMB values as yet ought to be evaluated in relation to all of the 4 Lewis standards. Consideration should here be taken to the degree of overweight and to the signs of endocrine dysfunction and hypothyroid symptoms should carefully be sought for.

Twenty-three Fröhlich-like cases (Type C) are in regards to weight and height entirely conformable to the large group of obese children (Type B). When the BMB values of these cases are referred to the Lewis standards for the surface area no significant deviation from the normal is demonstrable. The scatter may perhaps appear to be somewhat dispersed but the number of cases is too small to allow of a definite conclusion. The Fröhlich-like cases thus show no definite signs of increased or lowered basal metabolism and are in their main characteristics similar to the large main group of diffuse obesity.

One case of the *pluriglandular* group (Type D) shows normal BMB values in relation to all of the Lewis standards.

Some cases of different types were treated with thyroid hormone immediately prior to admission to the hospital. Thirty-two BMB determinations were made on these cases. Referred to the Lewis standards for the total surface area the values show a definitely increased basal metabolism. In approximately one-half of the cases the values fall above the upper limit for the normal range (+18%); all but 2 cases of the remainder fall above the normal mean value. The BMB value is on an average increased approximately 20 %.

Immediately prior to the BMB determination one boy received a series of 10 injections of gonadotropins of the serum from pregnant mares (Antex Leo). His basal metabolism was in good agreement with that of the thyroid-treated children.

Summary of basal metabolism in obese children.

The total basal metabolism of obese children is increased in relationship to chronologic age as well as to height age. This is the expression of the presence of a greater amount of heat producing tissue than is normal. Referred to the normal standards of Lewis et al. the total surface area standard, regardless of the degree of

overweight, gives the best agreement for the majority of the obese children. Also the Fröhlich-like cases show a normal basal metabolism. The early puberty and early pre-puberal acceleration of growth seem to be paralleled by a precocious onset of the pre-puberal changes of heat production. The adipose tissue of obese children seems to participate actively in the metabolism of the body. Thyroid treatment of obese children increases the basal metabolism.

CHAPTER VI.

Glucose tolerance.

Material.

Glucose tolerance tests have been carried out on the majority of the cases of the present obesity material. As hereby various laboratory technicians have participated in the tests a considerable personal error in method has arisen. The author has therefore personally carried out 20 glucose tolerance tests. It was seen that in the remainder of the series the curves obtained in about 100 cases were in good agreement with the 20 curves of the author. The two groups have been treated separately.

Methodics.

The tests have been started in the morning after a fasting period of approximately 14 hours. After taking samples for fasting blood sugar the children have received a 10 per cent glucose solution per os. The glucose dose has been 1 gm glucose per kg bodily weight (absolute weight). Every 30 minutes during the following 4 hours blood and urine samples have been taken and in the 20 tests of the author duplicate blood samples were taken. The children have all the time been in bed. The blood sugar has been determined according to the method of Hagedorn-Jensen and the urine has been tested for urine sugar according to Almén and for acids according to Legal.

The actual fasting value has been taken as basis for the evaluation of the tolerance curve, and the deviation of the maximum blood sugar value from resting level, i.e. the maximum rise of blood sugar, has been used for the determination of the tolerance. A maximum rise of blood sugar $<35~{\rm mg}$ % has been considered to show a high tolerance, 35—80 mg % a normal tolerance and $>80~{\rm mg}$ % a low tolerance.

Among the 20 specially tested cases of obesity (8 boys and 12 girls) 17 cases belonged to diffuse obesity, Type B (cf. p. 43), 1 case belonging to Type B I and 16 cases to Type B II (0—1 and > 1 obese individual in the family, respectively). In 3 cases there was Fröhlich-like obesity, Type C. The ages ranged from 4 to 13.

The mean value of the fasting blood sugar for these 20 cases was 94.9 ± 4.0 mg % with a variation of 62-128 mg %, thus approximately ± 33 mg %. This mean value is slightly higher than that of Svensgaard for normal children and that of Gordon for obese children. There is very good agreement with reference to the values of normal adults. The distribution for the 20 obese children is similar to that of normal children and adults.

The glucose tolerance curve had in these cases a maximum blood sugar value which in but 1 case exceeded 170 mg %. The time taken for the curve to return to the resting level showed a trend towards prolongation. In 55 % of the curves the time of return was $\leq 2\frac{1}{2}$ hours; in 40 % it was $2\frac{1}{2}$ —4 hours and in 5 % it was > 4 hours. Almén and Legal tests were negative in all of the cases.

The glucose dose has been determined according to absolute bodily weight. Calculated according to ideal weight the glucose dose in these cases amounts to max. 1.9 gm/kg bodily weight. The prolonged time taken for the return to resting level can thus hardly be explained by the factor that the children have received too great an amount of glucose (cf. p. 26), nor does the material show any correlation between the glucose dose in gm/kg bodily weight (ideal weight) and the time of return to resting level.

In all of the 20 cases of obesity there is a normal glucose tolerance. The 3 cases of Fröhlich-like obesity thus show a normal tolerance, which is not in agreement with the reports in the literature, where a high glucose tolerance is reported as the usual in these cases.

The children's food consumption in the hospital has been weighed meal by meal and recorded. On the basis of the recipes used in preparation of the food the carbohydrate consumption has been calculated and expressed in cal/kg bodily weight (absolute weight). Similar to normal children the obese children show at rising age (fig.

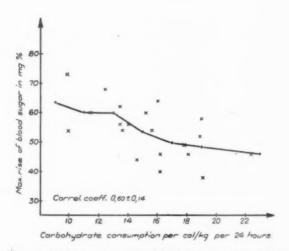


Fig. 11. Max. rise of blood sugar at peroral glucose tolerance test in 20 cases of obesity in relationship to the carbohydrate consumption expressed in cal/kg bodily weight (absolute weight) per 24 hours. As the cases belong to a restricted age group the differences in carbohydrate consumption in various ages are not taken into consideration.

obese case.
 means of obese children.

12A) a decreasing consumption of carbohydrates expressed in cal/kg bodily weight. Out of the 20 cases in question 18 cases belonged to a limited age group (8—12 years) and the decrement of the consumption in this period of life is negligible (approx. 3.5 cal/kg bodily weight per 24 hours). The values for the carbohydrate consumption of the 20 children are therefore, on the whole, mutually in agreement.

In fig. 11 are depicted the values for the carbohydrate consumption plotted against the correspondent values for the maximum rise of the blood sugar curve. There seems to be a correlation between the values for the carbohydrate consumption and the maximum rise of the blood sugar, but the dispersion is rather great. The correlation coefficient $r=0.60\pm0.14$ suggests that also other factors than the carbohydrate consumption influence the maximum rise of blood sugar. The varying degree of physical activity of the children may possibly be such a factor.

The group of 100 cases of obesity (46 boys and 54 girls) was composed of 90 cases of obesity Type B (23 cases of Type B I and 67 cases of Type B II), 6 cases of Type C, 1 case of Type D and 3 cases of Type E (cf. p. 43). The ages ranged between 2 and 15 years.

The average fasting blood sugar value for the 100 obesity cases was 98.0 \pm 1.6 mg % with a variation of 64—134 mg % or approximately \pm 35 mg %. These values are in agreement with those obtained for the 20 specially investigated cases of obesity.

The glucose tolerance curve had in several cases maximum values exceeding 200 mg %. The time of return here also showed a trend towards prolongation. In 35 % of the cases the time of return was $\leq 2\frac{1}{2}$ hours, in 60 % it was $2\frac{1}{2}$ —4 hours and in 5 % of the cases it was > 4 hours.

The maximum size of the glucose dose in these cases, calculated in gm/kg bodily weight (ideal weight) has here as well as in the 20 specially investigated cases been 1.9 gm/kg bodily weight. There is no correlation between the size of the glucose dose expressed in gm/kg bodily weight (ideal weight) and the length of time of return. The result shows that not in these cases either can the prolonged time of return be explained by the administration of an excessive amount of glucose.

The Almén test was in 2 cases positive during the first hour following the glucose intake. In both of these cases the maximum blood sugar exceeded 200 mg %. Legal was positive in 1 case.

The degrees of tolerance had the following distribution: high tolerance in 8 % of the cases, normal tolerance in 58 % of the cases and low tolerance in 34 % of the cases. There is no significant difference between different types of obesity or between the sexes. Cases of Fröhlich-like obesity showed normal tolerance in 4 cases and low tolerance in 2 cases.

The distribution of the degrees of tolerance in the present material shows no significant nor probable trend on comparison to the chronologic age, the degree of overweight and the age of the obesity. Reports in the literature relevant to these conditions in adults are not in correlation with the findings in the present material of obese children.

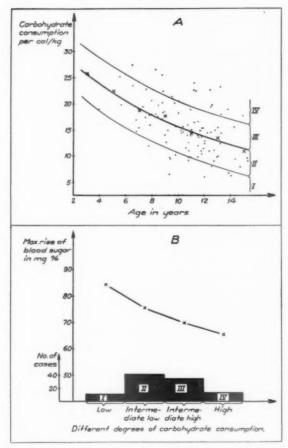


Fig. 12. A. Carbohydrate consumption in cal/kg bodily weight (absolute weight) per 24 hours in various ages in 100 cases of obesity.

- obese case. x mean value of biennial group.
- mean values (M) in different ages.
- mean values \pm 5 cal/kg (M \pm 5) in different ages.
 - I = Low carbohydrate consumption, < (M-5) cal/kg.
- II = Intermediate low carbohydrate consumption, (M-5)-M cal/kg. III = Intermediate high carbohydrate consumption, M-(M+5) cal/kg.
- IV = High carbohydrate consumption, > (M + 5) cal/kg.
 - B. Relationship between max. rise of blood sugar at peroral glucose tolerance test and carbohydrate consumption in 100 cases of obesity.
- I-IV = Cases with various degrees of carbohydrate consumption according

The diagram seems to show that a low carbohydrate consumption gives a greater max. rise of blood sugar at peroral glucose tolerance test than does a high carbohydrate consumption.

The material has been treated with consideration to the relationship between the carbohydrate consumption and the maximum rise of blood sugar, i. e. the glucose tolerance. The mean values for the carbohydrate consumption have been computed for different ages. The carbohydrate consumption in these cases decreases from approximately 25 cal/kg bodily weight (absolute weight) per 24 hours in age 3 to approximately 12 cal/kg bodily weight per 24 hours in age 15 with the variation approximately + 10 cal/kg bodily weight in different ages (fig. 12 A). The maximum rise of the blood sugar is therefore not directly comparable with the absolute figures for the carbohydrate consumption in cal/kg bodily weight. The cases are therefore divided into 4 groups according to the carbohydrate consumption with the mean values of the carbohydrate consumption (M) and $M \pm 5$ cal/kg bodily weight as border limits. The mean values for the maximal rise of the blood sugar curve have been determined for each group (fig. 12 B). The dispersion around the means is rather wide. As was to be expected the diagram shows that the maximum rise of blood sugar decreases in obese children also, i. e. the glucose tolerance rises with increasing carbohydrate consumption. This is in agreement with the results in the 20 specially investigated cases of obesity.

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Summary of glucose tolerance in obese children.

The fasting blood sugar value in obese children is in agreement with or negligibly higher than in normal adults and children. The variation of the fasting value is also the same as in normal individuals.

The glucose tolerance test in obese children shows a clear trend towards prolonged time of return to resting level which has been shown not to be due to the amount of glucose administered. For the rest the curve is on the whole in agreement with the tolerance curve of normal individuals.

Neither the age of the child nor the type, degree and age of the obesity influence the degree of the tolerance in the present obesity material. There is, on the other hand, here as well as in normal adults a correlation between the carbohydrate consumption and the glucose tolerance.

CHAPTER VII.

Sella turcica.

Normal material for the profile surface of sella turcica on the roentgenogram.

As the normal values of the literature for the profile surface of sella turcica on the roentgenogram are extremely variable (fig. 13) and as the limit values are not statistically computed, an own normal material was collected.

Material and methodics.

The sella turcica surface was determined according to the method of Haas (cf. p. 29) on 736 roentgenograms of cases with concussion of the brain or with fractures of the bones of the skull in the ages 0 to 30 years from Kronprinsessan Lovisa's Children's Hospital and the Serafimer Hospital. Consideration was taken to the median sella profile according to Bokelmann. The x-ray technic was identical in both hospitals. The distance focus-film varied between 60 and 70 cm, this having an influence of 2 to 3 % in the size of the roentgen picture. In a sella turcica with a 60 mm² surface this makes a difference of 1.2 to 1.8 mm². This is trivial as the normal distribution is 20 to 30 times greater.

On determination of the author's error of method with the surface-computing method of Haas a variation coefficient of 0.71-0.82~% was obtained.

Results.

The values of the author's normal material are seen in tables 11 and 12 and in figs. 13 and 14. The values have a normal distribution (fig. 16 A) and are similar for both sexes. Successive means have been computed for the border values $M+2\sigma$ and $M+2.5\sigma$.

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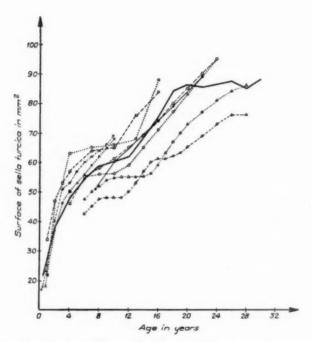


Fig. 13. Normal values of the profile surface of sella turcica on the roentgenogram according to the literature and the author's investigation.

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Fig. 13 shows that the results are in fairly good agreement with the previously reported values of HAAS.

The sella surface (contour of bone) very rapidly increases in size during the first 12 months of life. The mean value is at 0—3 months 12.0 mm², at 3—6 months 21.2 mm², at 6—9 months 22.6 mm² and at 9 months — 1 year 28.5 mm². The rapid increase of the roentgenologic sella surface, i. e. the surface outlined by the

Table 11. Normal values for the profile surface of sella turcica on the x-ray from 0-30 years, inclusive. Biennial groups.

0	No. of cases	cases Value (M)		$M \pm 2 \sigma$ 52.7 —9.3		Successive means of $M \pm 2 \sigma$		Successive means of $M \pm 2.5 \sigma$	
0-1	18								
1-2	61	38.0	5.7	49.4	26.6	53.1	27.1	56.4	23.8
3-4	59	47.9	4.6	57.1	38.7	56.4	36.3	58.9	33.8
5-6	52	54.4	4.7	63.8	45.0	62.8	43.8	65.2	41.4
7-8	51	58.5	5.0	68.5	48.5	68.5	47.0	71.3	44.3
9-10	58	60.2	6.3	72.8	47.6	72.0	48.3	75.0	45.3
11-12	45	61.9	6.5	74.9	48.9	77.9	48.4	81.6	44.6
13-14	40	68.7	9.9	88.5	48.9	86.7	50.8	91.2	46.3
15-16	46	75.5	10.6	96.7	54.3	100.6	51.9	106.7	45.7
17-18	42	84.2	16.1	116.4	52.0	107.9	55.7	114.5	49.2
19-20	45	86.1	12.7	111.5	60.7	114.4	56.1	121.7	48.8
21 - 22	47	85.3	15.0	115.3	55.3	114.1	57.8	121.2	50.7
23-24	42	86.5	14.5	115.5	57.5	114.9	57.9	122.0	50.7
25-26	43	87.4	13.2	113.8	61.0	112.9	59.8	119.5	53.1
27-28	45	85.1	12.2	109.5	60.7	109.7	63.8	115.4	58.1
29-30	42	87.8	8.9	105.6	70.0			_	account.

 $M \pm 2 \sigma$ includes 95.5 % of the material.

 $M \pm 2.5 \,\sigma$ includes 98.8 % of the material.

bone, during this period of life is associated with the ossification of Dorsum sellae, incomplete at birth but progressing successively during the first year of life. As the variation in the size of the sella surface in the group 0—1 year is considerable the assessment of the size of the sella surface can not be done with much certainty until after the age of 1.

It appears from fig. 14 that the curve of the mean values does not show any difference between boys and girls up to the age of about 8. At this age the sella surface of the girls commences to increase in size more rapidly than that of the boys. This is coincident with the time for the onset of prepuberty in the girls. A couple of years later the sella turcica of the boys also begins to increase more rapidly, in correspondence with the later onset of their prepuberty. Hereafter the two curves follow each other, the sella surface of the girls all the time being 3—7 mm² greater than that of the boys. In the age-group 20—30 years the difference between the curves appears to be 7—9 mm².

The limits of the distribution in the author's material are up

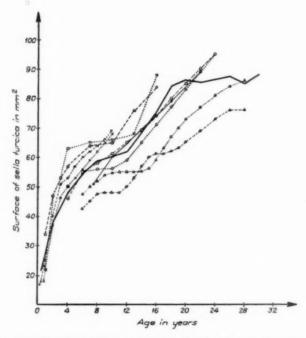


Fig. 13. Normal values of the profile surface of sella turcica on the roentgenogram according to the literature and the author's investigation.

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Fig. 13 shows that the results are in fairly good agreement with the previously reported values of HAAS.

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Table 11. Normal values for the profile surface of sella turcica on the x-ray from 0-30 years, inclusive. Biennial groups.

Age group	No. of cases	Mean value (M)	σ	$M\pm 2\sigma$		Successive means of $M \pm 2 \sigma$		Successive means of $M \pm 2.5 \sigma$	
	18	21.7	15.5	52.7	-9.3	_		_	
1-2	61	38.0	5.7	49.4	26.6	53.1	27.1	56.4	23.8
3-4	59	47.9	4.6	57.1	38.7	56.4	36.3	58.9	33.8
56	52	54.4	4.7	63.8	45.0	62.8	43.8	65.2	41.4
7-8	51	58.5	5.0	68.5	48.5	68.5	47.0	71.3	44.3
9-10	58	60.2	6.3	72.8	47.6	72.0	48.3	75.0	45.3
11-12	45	61.9	6.5	74.9	48.9	77.9	48.4	81.6	44.6
13-14	40	68.7	9.9	88.5	48.9	86.7	50.8	91.2	46.3
15-16	46	75.5	10.6	96.7	54.3	100.6	51.9	106.7	45.7
17-18	42	84.2	16.1	116.4	52.0	107.9	55.7	114.5	49.2
19-20	45	86.1	12.7	111.5	60.7	114.4	56.1	121.7	48.8
21 - 22	47	85.3	15.0	115.3	55.3	114.1	57.8	121.2	50.7
23 - 24	42	86.5	14.5	115.5	57.5	114.9	57.9	122.0	50.7
25 - 26	43	87.4	13.2	113.8	61.0	112.9	59.8	119.5	53.1
27 - 28	45	85.1	12.2	109.5	60.7	109.7	63.8	115.4	58.1
29 - 30	42	87.8	8.9	105.6	70.0	-	-	_	-

 $M\pm 2\,\sigma$ includes 95.5 % of the material. $M\pm 2.5\,\sigma$ includes 98.8 % of the material.

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It appears from fig. 14 that the curve of the mean values does not show any difference between boys and girls up to the age of about 8. At this age the sella surface of the girls commences to increase in size more rapidly than that of the boys. This is coincident with the time for the onset of prepuberty in the girls. A couple of years later the sella turcica of the boys also begins to increase more rapidly, in correspondence with the later onset of their prepuberty. Hereafter the two curves follow each other, the sella surface of the girls all the time being 3-7 mm² greater than that of the boys. In the age-group 20-30 years the difference between the curves appears to be 7-9 mm².

The limits of the distribution in the author's material are up

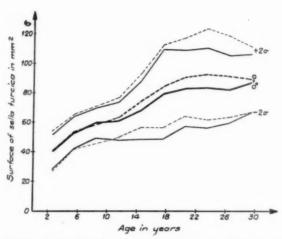


Fig. 14. Normal mean values of the profile surface of sella turcica on the roent-genogram for boys and girls, and the border-lines $M\pm 2\,\sigma$.

The diagram shows no difference between boys and girls up to the age of approx.

8. After that age the mean values of the girls are greater than those of the boys.

There is the same relation in adults.

to the age of 16 in fairly good agreement with the limit values of the literature. After this the limits are wider in the material of the author.

Summary of the normal material for the profile surface of sella turcica on the roentgenogram.

A normal material of the profile surface of sella turcica on the roentgenogram according to the method of Haas is described. Due to the wide normal variation in the group 0—1 year it is well-advised not to assess the profile surface of sella turcica on the roentgenogram until after the age of 1 year. The mean values of the size of sella turcica during growth do not show any differences between boys and girls up to the age of about 8. In girls over 8 years the sella values are 3—7 mm² greater than in boys of comparable ages. Also in adults in the ages 20—30 years the females seem to have values 7—9 mm² greater than the males.

Table 12. Normal values for the profile surface of sella turcica on the x-ray for males and females from 1-30 years, inclusive. Triennial groups.

Age group	No. of cases	Mean value (M)	σ	$M\pm 2\sigma$	Sussessive means of $M \pm 2 \sigma$
Males					
1-3	1 55 1	40.0	6.1	1 52.2 27.8	1
4-6	55	52.9	5.5	63.9 41.9	62.0 39.8
7-9	58	59.4	5.1	69.6 49.2	69.2 46.4
10-12	58	60.8	6.5	73.8 47.8	75.7 48.5
1315	39	68.0	9.8	87.6 48.4	87.5 48.2
16-18	36	79.1	15.2	109.5 48.7	102.2 51.9
19 - 21	46	83.1	12.9	108.9 57.3	109.7 54.7
22 - 24	47	83.7	13.5	110.7 56.7	108.4 57.9
25 - 27	41	82.7	11.4	105.5 59.9	107.7 61.4
28-30	48	86.9	9.8	106.5 67.3	
Females					
1-3	34	40.1	6.8	1 53.7 26.5	
46	28	53.5	5.8	65.1 41.9	62.0 36.6
7-9	22	58.2	6.3	70.8 45.6	69.8 45.1
10-12	16	63.3	6.7	76.7 49.9	80.7 50.8
13-15	23	74.7	9.1	92.9 56.5	97.8 55.1
16-18	30	84.7	14.0	112.7 56.7	107.9 58.7
19-21	21	90.7	13.3	117.3 64.1	117.1 60.4
22-24	20	92.7	15.4	123.5 61.9	119.7 63.3
25 - 27	25	91.2	13.7	118.6 63.8	118.4 64.0
28-30	16	89.4	11.2	111.8 67.0	

Investigation on the relationship hypophysis-sella turcica in children.

In the growing child there is a successive increment of the hypophysis as well as of the sella turcica and the growth curves follow each other. In order to ascertain if there in children is a correlation between the profile surface of the sella turcica on the roentgenogram and the correspondent hypophysis an investigation on necropsy material has been carried out.

Material and methodics.

The material comprises 27 cases in ages 1 to 16 years. The causes of death have been various. Such cases have not been included in which a prolonged rise of intercranial pressure, hypophyseal diseases or endocrine disturbances have been present.

In order to x-ray the sella turcica the bone around this has been excised whereby the hypophysis has been allowed to remain in the specimen. This has then been mounted in a stand after which the sella has been x-rayed. The relation focus-film has corresponded exactly to the position of the sella at the skull x-rays in vivo. The hypophysis has been prepared free and has been weighed suspended in a sensitive analysis balance. In order to determine the volume the hypophysis, still suspended in the balance, has been emerged in petroleum ether (sp. gr. 0.623). The weight of the fluid displaced has been determined and through this the bulk of the hypophysis has been computed. The volume figure in mm³ obtained has been compared to the correspondent sella surface computed according to the method of Haas (cf. p. 29).

Results.

The relationship between the surface of sella turcica and the correspondent hypophysis volume of these 27 cases appears from fig. 15 A. If the logarithm values for the volume of the hypophysis are calculated, a linear relation to the surface of sella turcica is obtained (fig. 15 B).

The regression equation is: y = 0.012 x + 1.61;

where y= the volume of the hypophysis in log mm³ and x= the profile surface of sella turcica in mm². The regression coefficient = 0.012 ± 0.001 and the correlation coefficient = 0.92 ± 0.003 .

It clearly appears from the diagram that the volume of the hypophysis and the profile surface of sella turcica on the roent-genogram in regard to the lower values are in good agreement, which was to be expected a priori. In the higher values of the sella turcica surface the values of the correspondent hypophysis clearly show a greater dispersion, but the number of cases is too limited to allow of any definite conclusions. It is the intention of the author to continue this investigation in order to throw further light on these conditions.

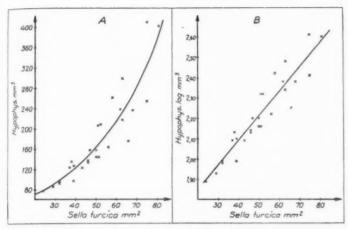


Fig. 15. Relationship in 27 cases between profile surface of sella turcica on the roentgenogram and the volume of the correspondent hypophysis.

The regression equation is:

$$y = 0.012 x + 1.61;$$

where y= the volume of the hypophysis in log mm³ and x= the profile surface of sella turcica in mm². The correl. coeff. = 0.92 ± 0.003 .

Small sella values have correspondently small hypophyses while greater sella values are corresponded by more varying values for the hypophyses.

Summary of the relationship hypophysis-sella turcica in children.

The relationship between the roentgenological surface of sella turcica and the correspondent hypophysis volume in children is in good agreement in regard to the lower values of sella turcica, while there seems to be a greater dispersion in regard to the higher values.

Sella turcica in obesity.

Material and methodics.

The obesity material on which the size of the sella turcica has been determined includes 350 obese children (170 boys and 180 girls). The sella values for children under 1 year have not been

included owing to the unreliability of the normal values of the sellas in age group 0—1 year (cf. p. 80).

On the basis of the age at the onset of obesity (fig. $2\,\mathrm{p}$. 49) the material has been divided into two groups. Cases which have become obese at 0-5 years have been referred to one group and cases which have become obese at ≥ 6 years to another. Those cases in which the child according to reports has become obese immediately subsequent to a disease have been treated further. The initiating diseases reported have been extremely varying (cf. p. 52).

The procedure in determination of the surface has been the same as that followed in the determination of the normal material. As basis for the comparison the normal values of boys and girls divided into triennial groups have been used (table 12). The deviation of the sella size of the obese children from the normal mean value in different ages and sexes has been expressed by the distribution of the cases in different classes with the limits: normal mean value M), $M \pm 1$ σ , $M \pm 2$ σ and $M \pm 3$ σ (cf. fig. 16). Successive means have been used for these limit values.

Results.

As a sex-linked difference is not present the sella turcica values of the boys and the girls have been combined. In fig. 16 is shown the distribution of the sella turcica values of the normal and of the obese children.

The distribution of the sella turcica values of 22 children with diffuse obesity of Type B I (cf. p. 43), in which the obesity has debuted prior to the age of 6, is seen in fig. 16 C. The diagram shows that all but 2 of the sella values fall below the mean value of the normal material and strikingly many below the border-line $M-2\,\sigma$. In fig. 16 D is seen the distribution of the sella values in 31 cases of obesity of Type B I in which the onset of obesity occurred after the age of 6. The values here are assembled around the normal mean value with a scatter which mainly falls above the line, although also below. The dispersion is greater than that of the normal material.

The sella values in diffuse obesity Type B II (246 cases) show the same distribution irrespective of age at the onset of obesity (fig.

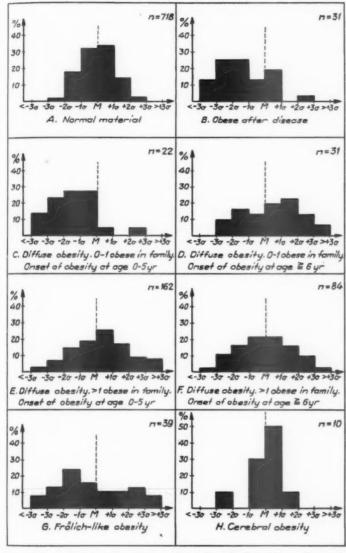


Fig. 16. Percentual deviation of the profile surface of sella turcica on the roentgenogram in normal children and in different types of obesity in children.

n =number of cases.

M and dotted line = mean of normal case material.

Classlimit = standard deviation (σ) of the different age groups (cf. tab. 12 p. 83) in the normal case material.

16 E, F). Here also the majority of the values are grouped around the normal mean value. The dispersion towards pathologically low and high values, respectively, is striking.

Cases with gigantism (14 cases) and dwarfism (6 cases) show a distribution of sella values in which the former have a trend towards high values and the latter a trend towards low values, but the number of cases is too limited to allow of a definite judgement. The majority of the values fall within the limits of the normal variations. The trend in both groups towards a divergent distribution may be explained by the different bodily proportions of these cases of the same chronologic age.

In 39 cases of *Fröhlich-like obesity*, Type C, the sella distribution shows that many values are low but that there also is an occurrence of high values. The dispersion is greater than normal (fig. 16 G). The classical picture of a large sella with a widened sella entrance was not found in any instance.

Ten cases of *cerebral obesity* show a sella distribution (fig. 16 H) which corresponds to that of the normal material. Another 2 cases of cerebral obesity with the presence of birth trauma with imbecility show extremely low sella values. This is probably explained by the physical and mental retardation of growth caused by the brain lesion.

In 31 out of the above 350 cases of *obesity* the adiposity according to reports has debuted in immediate *connection with-a disease* ("non-cerebral"). These cases show an accumulation of the majority of the sella values clearly below the mean values of the normal material (fig. 16 B). The occurrence of low sella values thus seems to be characteristic for these cases.

Especially apparent from the above diagram on the size of the sella turcica in obesity in children is the common occurrence of as well large as small sellas. The wide dispersion of the cases outside the limit values of the normal material suggests the possibility that some of the types of obesity (Type B I, B II and C, cf. p. 43) are not homogeneous but that they consist of at least 2 groups, each with its own mean around which the scatter is distributed. Factors of importance in all of the cases are, apparently, the occurrence of a disease prior to the onset of obesity and, in cases of Type B I, the age at the onset of obesity.

As appears from fig. 15 (cf. p. 85) small sellas seem to have correspondently small hypophyses. In these cases the possibility of an association between obesity and an insufficient hypophyseal function is conceivable.

Summary of sella turcica in obesity in children.

The profile surface of sella turcica on the roentgenogram in obesity in children shows on comparison with the author's normal material certain characteristic traits. Cases of all types of obesity which according to reports have debuted in association with disease as well as those cases of diffuse obesity with 0 to 1 obese individual in the family (Type B I), in which the obesity has debuted prior to the age of 6, show a distinct skewness in the size of the sella surface towards low values. The remainder of the cases of diffuse obesity show mean values correspondent to the normal, but with a dispersion which markedly exceeds the normal distribution. The Fröhlich-like cases show an accumulation of the sella values below the normal mean value, but here also there is a distribution with far too great a dispersion. Cases of cerebral obesity show sella values which lie close to the normal mean value, but the number of cases is too small to allow of a definite opinion.

CHAPTER VIII.

Skeletal development.

Material and methodics.

In 283 cases (124 boys and 159 girls) of the present obesity material 301 determinations of the skeletal age were done (132 in boys and 169 in girls). The normal standards for boys and girls of Lurie, Levy & Lurie (1943) were used. The determinations of the skeletal age and the height age were done within a range of 6 months.

Those cases whose height fell below the lowest values of Broman, Dahlberg & Lichtenstein's height tables (15 cases) were not included, as the height age of these cases could not be determined. Those cases also were excluded, in which the height age according to the tables indicated the age of > 20 (6 cases), their condition no longer being comparable with that of a growing individual.

In 60 per cent of the cases the assessment of the skeletal age was determined by the development of three bodily regions (handfoot-cubitus), in 23 per cent from two (hand-elbow or hand-foot) and in 17 per cent from one region only (hand). Occasional cases in which only the hand was x-rayed were excluded, as either the highest or the lowest border value for the skeletal age could not be determined.

Untreated and treated cases as well as various types of obesity dealt with separately.

Results.

Untreated cases of diffuse obesity, Type B (cf. p. 43), show for both sexes a skeletal age which clearly exceeds the chronologic age (254 determinations). The result is illustrated by fig. 17. There is no difference between obesity of Types B I and B II.

On comparison between the skeletal age and the height age (= the age of the average child at the bodily height in question)

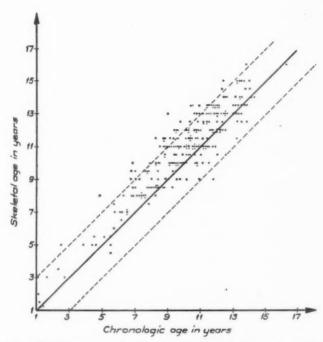


Fig. 17. Skeletal age versus chronologic age of untreated boys and girls with diffuse non-characteristic obesity.

The skeletal age is in advance of the chronologic age.

a very good agreement was obtained (fig. 18). The values fall within the range of variations indicated in the Lurie-standards (approx. $\pm\,2$ years). There is no sex difference nor difference between obesity of Types B I and B II.

Untreated children with diffuse non-characteristic obesity (Type B) thus show a skeletal age which, with a variation of \pm 2 years (= standard variation) is in agreement with the height age.

Those cases of obesity Type B, which correspond to giants (11 determinations) exhibit throughout a retarded skeletal age in relation to the height age (2 cases > 2 years in retard of the height age); the cases corresponding to dwarfs (4 determinations) show

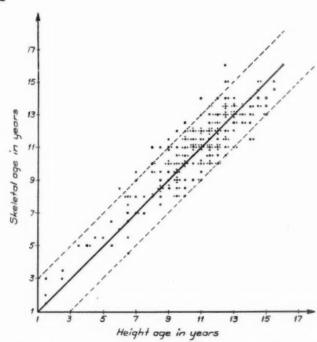


Fig. 18. Skeletal age versus height age of untreated boys and girls with diffuse non-characteristic obesity.

There is good agreement between skeletal age and height age.

an accelerated skeletal age (2 cases > 2 years in advance of the height age). This seems to indicate that skeletal development does not catch up with the rapid increase of height of the giants, while it in dwarfs on the contrary is in advance of their slower development. This circumstance should be considered in every case of abnormal bodily stature and should not allow of a premature opinion of a pathologically retarded or advanced skeletal development.

The skeletal development of the $Fr\"{o}hlich$ -like cases (Type C, 20 determinations) shows the same relation to the height age as that of the Type B cases of obesity.

In the pluriglandular group (Type D) 1 case has a normal skeletal age value.

The cases of *cerebral obesity* (Type E) have in 8 out of 10 determinations a skeletal age which is in very close agreement with the height age (\pm 0—1 year).

In 16 cases treatment with thyroid hormone has been pursued for 1 year or more. The treatment has been done unremittingly but the dosage has varied [Tabl. Thyreototal medium or forte "Astra" (= 0.18 and 0.54 mg org. iodine per tablet, respectively) 1 tablet 2 or 3 times daily]. The skeletal age in these cases shows the same distribution as that described above in untreated cases of obesity. The varying periods of time during which the treatment has been given do not seem to bring about changes in any definite direction.

Thus, the thyroid treatment of obese children in this material does not seem to influence the skeletal development in relation to the height age. In the presence of a hypothyroidism one would on the thyroid treatment of these cases expect an effect on the skeletal development.

Summary of the skeletal development.

The skeletal age (bone maturation) in obese children is in close agreement with the height age (\pm 2 years). In comparison with the chronologic age the skeletal age shows a marked acceleration, a circumstance which corresponds to the average excessive height of the obese children. The skeletal development of obese children ought therefore always to be assessed in relation to the height age.

With a few exceptions, the various types of obesity show, when compared with the height age, accordant results. Giants and dwarfs inasmuch as can be concluded from the few cases of the author, have a definite tendency towards a retarded skeletal development in the case of the former, with an accelerated development in the case of the latter. The skeletal development and the height development are in these cases obviously not parallel. This circumstance should be taken into consideration in cases of children with such abnormal bodily heights.

Treatment with thyroid hormone does in these cases not give any demonstrable changes of the skeletal development.

CHAPTER IX.

Prognosis.

The obesity material in the present investigation has in 328 cases been followed-up. As the treatment of the obesity in these children after hospitalization as a rule only has been carried out one or two months the majority of the cases may be considered as untreated at the reinvestigation.

The result of the follow-up investigation of the various types of obesity is described below.

Infantile obesity (Type A).

Of the 27 cases of infantile obesity (Type A) in the present obesity series 24 cases (17 boys and 7 girls) have been reinvestigated. They were all untreated. One-half of the reinvestigated children belonged to obesity Type A I and ther emainder to Type A II (cf. table 3 p. 42). The age at follow-up investigation has ranged from $1^{8}/_{12}$ years to 13 years, the mean being $6^{8}/_{12}$ years. During the first 5—6 years of this period the normal Rohrer-index values decrease rapidly. The Rohrer-index values of the obese children at reinvestigation are therefore not directly comparable to each other. The deviation of the values from those normal for comparable ages has therefore been expressed in multiples of the normal distribution (σ), which has transferred the values to largely comparable magnitudes.

Only 3 of the values expressed in this manner surpassed the limits + 3 σ and all of these belonged to obesity Type A II, i. e. with > 1 obese individual in the family. The remainder, especially cases of Type A I, were usually assembled within the limits \pm 2 σ from the normal mean value. The means of the deviations show for both sexes a difference between cases of Type A I and Type A II.

Cases of the latter type (A II) show the greatest deviation from the normal (boys + 1.1 σ and girls + 2.9 σ), while cases of the former type (A I) have the smallest deviation (boys + 0.4 σ and girls + 0.3 σ). The number of cases, however, is too limited to make the difference between the types statistically significant. The result, however, suggests that cases of Type A II during growth more commonly become more obese than do cases of Type A I.

At the reinvestigation 10 out of 11 cases of Type A I, where the reports with regard to the family history were adequate (cf. p. 42) and only 6 out of 12 cases of Type A II had been interpreted as "non-obese". This is in agreement with the facts related above.

Cases of infantile obesity should thus generally be interpreted as physiological extremes in which the obesity usually regresses during growth.

The poorer prognosis indicated for obesity cases Type A II (> 1 obese individual in the family) is in correlation with the result previously obtained on analysis of the obesity cases Types B I and B II (cf. p. 50). Type B II (> 1 obese individual in the family) showed, namely, on comparison with Type B I a greater frequency of early debuting obesity. These early debuting B II-cases are thus prolonged A II-cases, while cases of Type B I usually are not obese already in infancy.

In cases of obesity in ages 0—2 years — if it from these few cases of infantile obesity be permissible to draw any conclusions — the number of cases of obesity in the family thus affords a certain amount of guidance in the judgement of the child's further bodily development.

Diffuse non-characteristic obesity (Type B) and Fröhlich-like obesity (Type C).

The greatest portion of the present obesity material comprises children with obesity of Type B (diffuse obesity) and Type C (Fröhlich-like obesity). Here as well as in previous sections the cases in these groups will be combined when it is established that there is no difference between the groups at follow-up investigation.

As appears from fig. 3 (cf. p. 54) the obese children in this material usually are taller than normal children of comparable ages.

Table 13. Mean deviation from normal stature at hospitalization and at follow-up investigation in obese boys and girls. The table includes only those patients which at follow-up investigation were ≥ 20 years. Broman, Dahlberg & Lichtenstein's height tables for normal children have been used.

	H	lospitalization	Followed-up at age ≥ 20		
Group	n	Deviation from height standard in cm	n	Deviation from normal height at age 20 in cm	
		Obese boys			
I	25	1 + 4.7	14	+ 1.5	
11	12	5.8	23	+ 1.5 - 7.5	
*		Ob an alaba			
		Obese girls			
I	20	+ 5.4	10	1.7	
11	11	5.6	21	5.5	

n = number of cases.

Group I = cases taller than the values of the height standard for comparable ages.

Group II = cases shorter than the values of the height standard for comparable ages.

Between different types of obesity there is no difference in height. It is of interest to see the development of *stature* of these obese children in adulthood.

68 cases of Type B and Type C were at follow-up investigation ≥ 20 years of age. The cases were divided into 2 groups according to the height at hospitalization. Cases taller than normal for the age according to Broman, Dahlberg & Lichtenstein's height tables were referred to one group and cases shorter than the normal to another. The deviations from the respective normal heights were determined and the means of the deviations were determined for the two groups. Analogous groupings and determinations were done at the follow-up investigation.

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In the results there was no difference between boys and girls, between different types of obesity or between treated and untreated cases. In table 13 are set forth the combined values. It hereby appears that $^2/_3$ of the cases at hospitalization were taller than the normal average, while $^1/_3$ were shorter than the normal. At follow-up investigation in adulthood (≥ 20 years) the conditions are reversed.

Here ¹/₃ of the cases are taller and ²/₃ of the cases are shorter than the average adult (= 20 years) height according to the normal standards. This is in agreement with Shuttleworth's, and others reports (cf. p. 18) that children with an early puberal acceleration of growth attain a lesser absolute height than do cases with a later acceleration of growth. As the obese children throughout show an earlier average development than normal children (cf. Chapter IV) the obese children are best in correspondence with Shuttleworth's cases with an early bodily development. Children which at hospitalization were very tall, giants inclusive, and children which were very short, dwarfs inclusive, do, however, as adults appear to remain taller and shorter, respectively, than the normal average.

78 boys and 75 girls of the reinvestigated untreated cases of obesity Type B and Type C were at hospitalization 7—13 years of age. These cases were according to the age at the follow-up investigation divided into 3 groups, one group including ages 13—16 years (56 cases), one group including ages 16—20 years (44 cases) and one group including ages ≥ 20 years (53 cases). The ages in the ≥ 20 years group ranged from 20—35 years with an average age of $24^{10}/_{12}$ years for the males, of $24^{7}/_{12}$ years for the females and with $24^{8}/_{12}$ years for the entire group. The mean Rohrer-index values have been computed for the cases in these different groups and are recorded in fig. 19 A—B. No significant difference was demonstrable between the values of cases of obesity Type B or its subdivisions B I and B II, and Type C, wherefore the combined result is reported.

In fig. 19 have also been set forth the normal values for Rohrer's index in different ages according to Broman, Dahlberg & Lichtenstein's Rohrer-index table. This is valid for children and adoloscents up to age 19. For the evaluation of the Rohrer-index values of the patients ≥ 20 years at the follow-up investigation it is of essential importance to know the normal Rohrer-index value for comparable ages. As far as can be ascertained normal values have not as yet been published. By obtaining the Rohrer-index values of the material of normal-weight children's parents, collected for the investigation of heredity (cf. p. 45) and distributing

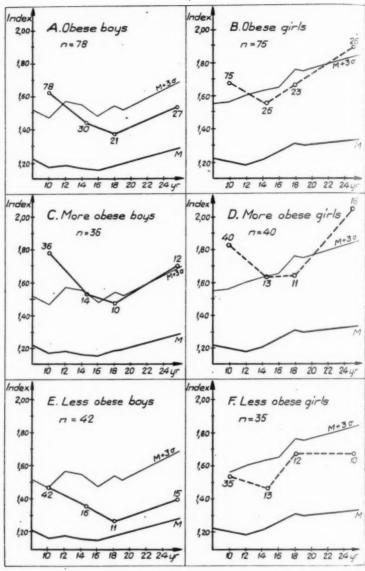


Fig. 19.

Table 14. Rohrer's index for normal children's parents in various ages.

Age yr	₫*			Q		
	n	σ	$M \pm \varepsilon (M)$	n	σ	$M \pm \varepsilon (M)$
21—25	0		_	0	_	
26-30	5	_	1.20	.7		1.42
3135	15	0.16	1.37 ± 0.04	37	0.19	1.37 ± 0.0
36-40	64	0.14	1.36 ± 0.02	73	0.22	1.48 ± 0.0
41-45	64	0.21	1.37 ± 0.03	68 .	0.22	1.50 ± 0.0
46-50	54	0.18	1.45 + 0.03	39	0.20	1.54 ± 0.0
51-55	23	0.11	1.45 ± 0.02	13	0.20	1.47 ± 0.00
56-60	6	_	1.43	2	_	1.22
> 60	8	_	1.42	0		

n = number of cases.

 $\sigma = \text{standard deviation}.$

 $M \pm \varepsilon (M) = \text{mean} \pm \text{standard error of the mean.}$

this in various age groups, a certain conception is obtained, despite the shortcomings of the material, with regards to the normal Rohrer-index values in adulthood. The result is seen in table 14. It appears that the values in ages 20—30 are too few in numbers to be representative and that not until the age of 31—35 and above this are the values statistically dependable.

In fig. 19 the normal Rohrer-index values for ages above 19 have been demarcated by a line which connects the Rohrer-index values for the 19-year-olds according to Broman, Dahlberg & Lichtenstein's normal standards with those of the 35-year-olds according to table 14. It should be pointed out that this line merely indicates the approximate size of the normal Rohrer-index values in ages

Fig. 19. A—B: Average Rohrer's index for untreated obese boys and girls, age 7—13 at hospitalization, which have been reinvestigated at ages 13—16, 16—20, or ≥ 20 .

C—F: The same material as in A—B divided into a more obese and a less obese group with the median of the Rohrer-index values at hospitalization as limit $(+3.5\sigma)$ according to Broman, Dahlberg & Lichtenstein's Rohrer-index table).

Normal curve (M) for Rohrer's index acc. to Broman, Dahlberg & Lichtenstein's Rohrer-index table and acc. to table 14.

 $⁻M + 3\sigma = \text{mean} + 3 \text{ times the standard deviation.}$

o Mean Rohrer-index value for obese boys and girls in age groups 7—13, 13—16, 16—20 and ≥ 20 . The numerals indicate the number of observations.

20—30, as exact values are lacking with regard to this period of life. There would not, however, seem to be any great deviation from the values indicated here, as calculations according to the normal-weight tables of insurance companies (i. e. "Hafnias tayle") on the whole give similar values.

It is in fig. 19 A seen how the average Rohrer-index values for the obese boys in the age groups 13—16 and 16—20 decrease successively, again increasing in age group ≥ 20 . The degree of increase is largely the same as the normal increase of the Rohrer-index value for comparable ages. The absolute figures for the average Rohrer-index values, however, are throughout considerably higher than the normal. In fig. 19 B are shown the correspondent average values for the obese girls. There is here a decrease of the index value only in age group 13—16, and thereafter a successive increase in age groups 16—20 and ≥ 20 . The increase of the index value in age group ≥ 20 is considerably greater than that which normally occurs. The absolute figure for Rohrer's index is in this group likewise considerably higher than the normal and higher than in the boys. The value is in approximate correspondence with the upper limit of the normal $(+3 \sigma)$.

The obesity in childhood thus after a marked reduction during and following puberty seems to increase anew and frequently again attains a greater or lesser development. The prognosis in adulthood for untreated cases of obesity thus is rather variable and for the obese girls considerably poorer than for the obese boys.

If the obesity material included in fig. 19 A—B is divided into a more obese and a less obese group with the median of the Rohrer's index at hospitalization as limit, and the mean Rohrer-index values are calculated for the same age groups as for the entire material fig. 19 C—F is obtained. Although the number of cases in each age group due to the subdivision is rather small, the results on the whole show the same trend as do the both groups combined (fig. 19 A—B). There seems to be, however, a definite difference between the absolute figures for Rohrer's index, i. e. for the degree of obesity. The children belonging to the more obese group are at age ≥ 20 still on the average more obese than are the children of the less obese group, the females exhibiting the greatest degree

of obesity. The children in the less obese group thus more commonly appear to have a better prognosis in adulthood. The boys in this group have a nearly normal Rohrer-index value, while the values of the girls are somewhat higher.

Those children who at ages 7—13 are less obese thus at \geq age 20 more frequently seem to have a better prognosis than do the more obese children and the less obese boys seem to have the best outlook.

The material, however, is too limited to allow of a definite opinion of the prognosis in adulthood for various types of obesity (B I, B II and C, cf. p. 43). In a larger material, however, there would probably appear a difference between Type B I and Type B II (diffuse obesity with 0-1 and > 1 obese individual in the family, respectively), owing to the difference in the degree of adiposity in these two types of obesity (cf. p. 55). Cases with obesity Type B I belonged in about 70 % to the less obese group of children, as against 47 % of the cases of Type B II. As was shown above, those children which at ages 7-13 are less obese have most frequently the best prognosis. Cases of Type B I should thus on the average have the best expectancies in adulthood. The number of cases of obesity in the family, which to some extent is an expression of the potency of the constitutional element, will probably therefore in a larger series of obesity in children be shown to be of importance for the prognosis in adulthood. This is also in agreement with the results of the investigation on heredity (cf. p. 46) which establishes that less obese children more commonly have less obese parents than do the more obese children.

In table 15 are set forth the mean values of the Rohrer-index at hospitalization and at follow-up investigation for the age groups of obese children shown in fig. 19. Furthermore the consumption of food has been assessed according to the food habitus reported at follow-up examination and has been considered as belonging to either of the following groups: absence of, possible, or marked luxus consumption. The mean Rohrer-index values for cases belonging to these groups have been determined and the difference between the Rohrer-index at hospitalization and at the follow-up investigation has been determined. The cases were distributed about equally between the various degrees of luxus consumption.

Table 15. Rohrer's index at hospitalization in ages 7–13 and at follow-up investigation in ages 13-16, 16-20 and ≥ 20 , respectively, for untreated cases of obesity in children, and also for different degrees of luxus consumption according to the food habitus at follow-up investigation. Also the difference between the Rohrer-index value at hospitalization and at follow-up investigation of the various groups.

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	Obese boys			Obese girls			
	n	Rohrer-index hospfollup	Diff.	n	Rohrer-index hospfollup	Diff.	
		7—13 yea 13—16 yea			tion and examination		
All cases	30	1.60-1.43	0.17	26	1.66-1.55	0.11	
1	. 9	1.59-1.27	-0.32	3	1.60-1.44	-0.16	
Luxus +	9	1.59—1.27 1.61—1.42 1.60—1.56	-0.19	13	1.65-1.49	-0.16	
+	12	1.60-1.56	-0.04	10	1.68—1.65	0.03	
		7—13 year 16—20 year					
All cases	21	1.62-1.37	-0.25	23	1.68-1.66	0.02	
1	6	1.50-1.27	-0.23	10	1.72-1.57	-0.15	
Luxus ±	13	1.50—1.27 1.66—1.36 1.74—1.73	0.30	4	1.69-1.63	-0.06	
+	2	1.74-1.73	-0.01	9	1.63—1.77	+0.14	
		7 —13 year ≥ 20 years a				1,	
All cases	27	1.63-1.53	0.10	26	1.72-1.90	+ 0.18	
1	4	1.59-1.39	-0.20		1.78-1.53	-0.25	
Luxus ±	12	1.59—1.39 1.63—1.50 1.66—1.63	-0.13	6	1.56-1.71	+0.15	
+	11	1.66-1.63	0.03	14	1.78-2.14	+0.36	

n = number of cases.

 $\mbox{Diff.} = \mbox{Difference}$ between Rohrer's index at hospitalization and at follow-up examination.

Luxus $\begin{array}{l} --=$ absence of luxus consumption. $\begin{array}{l} +=\end{array}$ possible luxus consumption. $\begin{array}{l} +=\end{array}$ marked luxus consumption.

The change of the Rohrer-index values, i. e. of the degree of the obesity, from the time of the hospitalization to the time of the follow-up examination, in the various degrees of luxus consumption shows nearly the same trend throughout for the different age groups and for both sexes. Cases with absence of luxus consumption decrease markedly in weight, cases with possible luxus consumption

decrease less, and cases with a marked luxus consumption decrease the least, or even increase their obesity. Despite the small number of cases this shows the importance of the diet for the degree of obesity and illuminates the importance of a proper diet in obesity in children as well as in adults.

The Fröhlich-like cases (Type C) showed, as already mentioned, with regard to changes in the degree of the obesity apparently the same conditions during development as the large group of obese children. The typical fat distribution, however, seems to regress gradually or to attain a more diffuse distribution. It is in these untreated Fröhlich-like cases of interest to follow the development of the external genitals. This has already been done in the discussion of the puberal development of the obese children (cf. p. 57). The investigation seemed to show that no difference between the large group of obese children (diffuse obesity) and the Fröhlichlike cases is demonstrable, and that, in the few cases of this series, at least no late development of puberty is established. This implies that the genital development even occurs probably somewhat earlier than in normal boys. Only in 1 case, a mentally retarded boy of 20 the genitals were not fully developed. All other cases older than 18 years showed a genital development which was entirely comparable with that of normal adults.

It is of interest to see whether there is any correlation from the prognostic point of view when the material is divided into two groups according to the age at the onset of obesity. No difference can here be demonstrated between the groups regardless of whether the limit for the onset of obesity is drawn at the age of 6 in both sexes, or at the age of 10 with regard to the boys and at the age of 8 for the girls. The number of cases which have reached adulthood, however, is too limited to allow of a definite judgement.

In Chapter VII was shown the common occurrence of very small as well as very large values for the profile surface of sella turcica on the roentgenogram. Whether the prognosis in adulthood is different in cases with different sella sizes can not be judged, as only 21 cases in which sella x-ray has been taken are ≥ 20 years at the follow-up investigation. In these few cases, however, the size of the sella appears to be non-essential for the prognosis.

The material of the prognosis investigation comprises only 53 individuals which at the follow-up investigation were $\geqq 20$ years, which is a relatively small group. A considerably larger number of cases is required in order to discuss with certainty the prognosis in different types of obesity. A renewed follow-up investigation of the present obesity material in about 10 years would throw further light on these conditions and will, circumstances permitting, be carried out.

Pluriglandular obesity (Type D).

Common to the 5 girls in this group is the occurrence of irregular menses, which also was the case at the time for the follow-up investigation at ages ranging from 18 to 32. One case later on had regular menses subsequent to pregnancy. Another case showed signs of virility with hirsute anomalies. Two of the cases showed signs of cerebral disturbance (retardation and epilepsy, and insanity, respectively).

Out of these 5 cases 4 were treated with thyroid hormone over a period of several years and a couple of the cases have furthermore been treated periodically with ovarial hormone. All of these cases are still, at the follow-up investigation, more obese than the normal, despite a treatment which at least in some of the cases has been energetically pursued. The number of cases, however, is too small to allow of any definite conclusions, but in 4 of the cases the obesity seems to be unusually resistant to therapeutic measures and the prospects for the prognosis seem gloomy.

Cerebral obesity (Type E).

Out of the 19 cases of cerebral obesity $^2/_3$ at hospitalization belonged to the more obese group of children. Out of these 19 cases 14 have been followed-up, at ages ranging from 4 to 35 years, with an average of 16 $^8/_{12}$ years. Hereby the majority of the cases (6 which at hospitalization were more obese and 3 which were less obese) have been more obese than the mean values for comparable ages of more obese and of less obese children, respectively, of Type B and Type C (cf. fig. 19 p. 98). Two out of these 9 cases have received dietary and thyroid treatment with no appreciable effects.

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Out of the 5 cases which at reinvestigation were thinner than the average for Type B and Type C no case showed a normal Rohrer-index, although 4 of these cases had been treated with diet and/or thyroid hormone during a prolonged period.

The cerebral cases of obesity seem, as far as can be concluded from these few cases, to have a poorer prognosis than the large group of obese children. Dietary and thyroid treatment during a prolonged period of time may possibly keep the obesity within moderate bounds.

Summary of the prognosis in obesity in children.

A follow-up investigation of the obesity material has been carried out in 328 cases.

The reinvestigation showed that cases of infantile obesity (Type A) as a rule should be considered as physiological extremes, in which the obesity in the majority of the cases regresses during development. In cases where obesity is present in > 1 case in the family (Type A II) the obesity is during development more liable to persist than in cases in which there is only 0-1 case of obesity in the family (Type A I).

The obese children with diffuse obesity (Type B) and Fröhlichlike obesity (Type C) are in adulthood (≥ 20 years) shorter, on the average, than the average height of normal 20-year-olds, according to Broman, Dahlberg & Lichtenstein's height tables. Children, which already during growth are very tall (giants) or very short (dwarfs) in adulthood also seem to be taller or shorter, respectively, than the average.

The obesity in the *untreated* obese children of these types (Type B and Type C) increases anew after a marked decrease during and after puberty, and frequently in adulthood again attains a greater or lesser development. The prognosis in adulthood thus is rather variable. Those girls which at hospitalization were 7—13 years of age, and belonged to the more obese group appear to have the poorest prognosis and the less obese boys appear to have the best prognosis. No difference between the types is demonstrable but the number of cases in each group is too small. Judging

by the case distribution within obesity of Type B I and B II (0–1 and >1 obese person, respectively, in the family) with consideration to the degree of obesity and also to the results of the heredity investigation, the knowledge of the number of cases of obesity in the family should be of value in the evaluation of the prognosis for the future development of the patient. Another factor of importance for the degree of overweight, regardless of the age of the patient, is the food habitus, i. e. the degree of luxus consumption.

The genital development of the Fröhlich-like children (Type () in puberty seems on the average to be similar to that of the large

group of obese children.

Cases of pluriglandular obesity (Type D) and cerebral obesity (Type E) are too few to allow of a definite judgement of the prognosis. These cases, however, seem to be remarkably resistant to therapy.

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CHAPTER X.

Therapy.

Material.

The present obesity material has been treated either with a partially restricted diet or with a diet of 1 000-1 200 calories, with thyroid hormone and in a few cases with hypophyseal hormones, sex hormones and chorionic gonadotropic hormone. The thyroid extract commonly used has been Thyreototal medium "Astra" (1 tablet 1-3 × daily) which contains 0.18 mg organic jodine per tablet. The treatment has as a rule been instituted on discharge from the hospital and supervision at the outpatient department has been arranged. The reduction of weight has not been allowed to take place too rapidly with the object, inter alia, of thereby perhaps obtaining a more permanent result. A reduction of weight of 0.5 kg per week has usually been sought. Commonly, however, the treatment was only pursued during some months, wherefore the effect of therapy in obesity in children can be discussed but incompletely; nor has the author intended to discuss the question of therapy in further detail. In the present work will only briefly be described the experience gained by the study of the treated cases of obesity.

Results.

Those cases which during several years have been treated according to the program outlined above are too restricted in number and too irregularly treated and checked to allow of a more thorough analysis.

By a comparison of the reduction of weight of the children treated during a short time a certain conception of the effect of the treatment may be obtained. Out of the 65 children in this group

Table 16. Effect of treatment of obese children expressed in overweight reduction in kg per month.

		of treatment months	Period of treatment 6 months—1 year		
Treatment	No. of cases	Overweight reduct. in kg/months	No. of cases	Overweight reduct. in kg/months	
Restricted diet	5	2.4	3	0.5	
Thyroid hormone	13	1.8	3	1.0	
Restricted diet + thyroid hormone	33	2.1	8	0,8	

which belonged to the group diffuse obesity (Type B) and Fröhlich-like obesity (Type C) 78 % were treated ≤ 6 months and the remainder between 6 months and 1 year. No differences could in this material be shown between the sexes or the different types of obesity. The combined results are shown in table 16. It appears from this, as was to be expected, that the effect of the treatment was greatest during the first months of treatment. Furthermore, there does not appear to be any significant difference between different methods of treatment: dietary treatment alone or hormonal treatment alone or combined dietary and hormonal treatment. The number of cases, however, is too restricted to allow of a definite opinion with regard to the greater or lesser effectivity of the various methods of treatment.

In several of the cases treated there are reports on weight and height after the termination of the treatment. Through these, and through the values obtained at the follow-up investigation of the author it clearly appears that the frequency of relapse is very great. An illustration of the effect of treatment and the tendency to relapse on the termination of treatment is seen in fig. 20. It also appears from individual cases that thyroid treatment alone at a continued abnormally great food consumption is incapable of producing more than a certain slowing of the increase of weight.

During a short period 7 cases were treated exclusively with hypophyseal hormones, sex hormones or chorionic gonadotropic hormone. No definite effect on the obesity has been demonstrable in these cases.

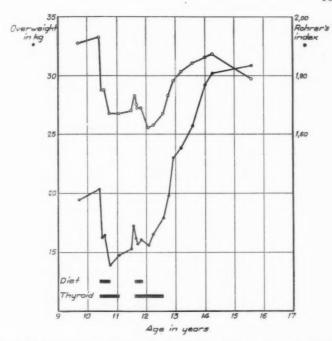


Fig. 20. Effect of treatment in Case No. 441. Treatment has consisted of restricted diet and Thyreototal medium "Astra", 0.18 mg org. iodine per tablet, 1 tablet 2—1 times daily. The effect is depicted by changes in Rohrer's index and in overweight expressed in kg. The height-weight tables of Broman, Dahlberg & Lichtenstein have been used.

It can not here be stated which treatment is the most expedient and correct in the case of obese children. For this is required a homogeneously treated and strictly supervised material, in which the influence of a number of various factors (dietary habitus, degree of activity, mentality, etc.) are taken into consideration. A satisfactory result, however, seems to be dependent on a satisfactory cooperation between the child, the parents and the physician.

The question in regard to the most expedient treatment of obesity in children is the object of an investigation by the author and will be discussed in a further publication.

Summary of therapy in obesity in children.

The treatment of obese children has been carried out with diet exclusively, thyroid treatment exclusively, or with combined dietary and thyroid treatment. The number of cases treated during a sufficiently long period of time is in the present material too restricted to allow of a definite opinion with regard to the greater or lesser efficacy of the different methods of treatment. Therapy seems, however, as was to be expected, to be most effective during the first months of treatment. The frequency of relapse is very great. Treatment with hypophyseal hormones, sex hormones or chorionic gonadotropic hormone alone seems, in the few cases observed in the present material, to be without influence on the obesity.

GENERAL SUMMARY.

The present series of obesity comprises more than 500 cases which have been hospitalized in one of the several children's hospitals of Stockholm. The present study is based on the results of the examinations carried out during hospitalization and of a number of supplementary examinations, and on the results of a follow-up examination of 328 of the cases.

In order to avoid, to the furthest extent possible, the large subjective component inherent to the division of the material most commonly employed in the literature, namely, the exogenousendogenous and the endocrine, the material has been divided into one very large group of 401 cases, in which a diffuse non-characteristic obesity is the only "symptom of disease", one group comprising 52 cases with marked Fröhlich-like obesity (Dystrophia adinoso-genitalis-like obesity), and three small groups including cases of infantile obesity, pluriglandular obesity and cerebral obesity. The two groups comprising diffuse obesity and infantile obesity have been divided into two subdivisions according to the number of cases of obesity in the family, 0-1 and > 1 obese individual, respectively (cf. Chapter II). In the group diffuse obesity are also included cases of gigantism and dwarfism (17 cases and 6 cases, respectively), in which the absolute bodily stature is the only factor that distinguishes them from the remainder of the group.

The occurrence of obesity amongst the parents of the obese children has been compared to this condition in the parents of normal children (cf. Chapter III). The obesity material has also been divided into a more obese, and a less obese group and has been analyzed from this viewpoint. It is found that the obese children more commonly have obese parents than do the normal children and the more obese the children, the more commonly are the parents more obese, thus especially the mothers.

In Chapter IV is described the development of the obesity and the physical and mental development of the obese children, as compared to normal children.

The treatment of the material shows that the age at the onset of obesity shows two peaks, one at the age 0-3 years, the other at the age 6-12 years. It further appears that cases of diffuse obesity with >1 obese individual in the family have a higher incidence of the onset of obesity before the age of 6 than do the cases with 0-1 obese individual in the family, while the reverse is the case in patients who have become obese after the age of 6 years. There is also in cases with different degrees of obesity a difference in the age at the onset of obesity. It is thus twice as common for the obesity in the more obese children, as compared to the less obese children, to debut prior to age 6.

As initiating causes to the obesity factors of cerebral and of non-cerebral character have been reported. The latter have been extremely variable in type and have, when the cases that "always" have been obese are excluded, been considered present in 18.9 % (44 out of 233 cases) of the material.

The obese children show a greater incidence of birth-weights exceeding 4 000 gm than do the normal children.

The height, weight and Rohrer-index (height-weight index of build) of the obesity material has been compared with the Broman. Dahlberg & Lichtenstein height-weight- and Rohrer-index tables for normal children. The height of the obese children in 74.4 % of the cases exceeds the normal and the bodily weight, assessed in relationship to the height, is in 85.2 % above the value for $+2\,\sigma$ and in 56.5 % above the value for $+3\,\sigma$ of the height-weight tables for normal children. The material expressed in Rohrer-index shows a curve of distribution in agreement with the weight distribution. The median lies at $+3.5\,\sigma$ and divides the material into one more obese and one less obese group of children. It appears that children with >1 obese individual in the family more commonly become more obese than children where obesity is absent or merely occurs in one case in the family.

The obese girls have on the average a menarcheal age of 13 years (120 cases), which is approximately 1 year earlier than that normal

for Swedish girls. Also the obese boys have probably on the average an earlier puberty. This also seems to be the fact in the Fröhlichlike cases but these, however, are too limited in number to allow of a definite opinion.

The onset of the prepuberal acceleration of growth of the obese children (27 cases) occurs already 4 years prior to the menarcheal age, which is roughly 1 year earlier than in normal children.

The development of intelligence has in 52 cases been tested according to the Terman-Merrill method. The intelligence age is in these cases advanced in relation to the chronologic age but is on the whole on a par with the height age.

The basal metabolism has been determined in 319 of the children and has been referred to the normal standards of Lewis, Duval & Hiff (cf. Chapter V).

The initial BMB value was in 68 % of the cases greater than the subsequent value. This is probably due partly to the elimination of a certain mental apprehensiveness, whereby a more "basal" state is attained in more excitable children and partly to a reduction of the food consumption in the hospital, this lowering the basal metabolism.

The standard metabolism of the obese children shows on comparison with the Lewis standard for total surface area a good agreement with a slight trend towards low mean values regardless of the degree of overweight. The distribution is the same as that of the normal standard, \pm 18 %. Referred to the standard for calories per hour per square meter surface area the mean values are lower, being lowest with reference to the weight standard. Referred to the height standard the values are considerably higher.

The total basal metabolism of the obese children is roughly 5 calories per hour greater than that of normal children of the same height and sex, which indicates an increase of active heat-producing tissue. The adipose tissue of these obese children seems also to participate actively in the metabolism of the body.

During puberty both boys and girls show a diminution of the annual decrease of the caloric metabolism expressed in calories per hour per square meter surface area. In comparison with normal children this change occurs earlier in obese children and at about the same time as the onset of the puberty and the prepuberal acceleration of growth of the obese children.

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In a few cases the BMB determinations have been carried out on children with giant and with dwarf stature, respectively. On comparison with the Lewis standard for total surface area which is not intended for such extremes of bodily build, there appeared also a trend towards low BMB values. Until further experience has been gained in such extreme cases, however, the BMB values ought to be evaluated in relation to all of the four Lewis standards.

Thyroid treatment increases the basal metabolism in the obese children on the average with about 20 %.

The blood sugar fasting values and the glucose tolerance of the obese children is discussed in Chapter VI.

The mean blood sugar fasting value of 100 obese children shows values (98.0 \pm 1.6 mg%) which largely are in good agreement with those of normal adults and children and the variation (\pm 35 mg%) is the same as in normal individuals.

The glucose tolerance curve shows in roughly one-half of the cases a prolonged time of return to fasting level which has been shown not to be due to the amount of glucose administered (max. $1.9~\rm gm/kg$ bodily ideal weight). For the rest, the curve is in agreement with the shape of the normal glucose tolerance curve.

The glucose tolerance in the obese children is not influenced by the age of the children nor by the type, degree or age of the obesity but there is on the other hand, as in normal adults, a correlation between the glucose tolerance and the carbohydrate consumption, the tolerance rises with increasing carbohydrate consumption. In 20 cases investigated further, the correlation coefficient is $r=0.60\pm0.14$, which suggests that also factors other than the carbohydrate consumption influence the glucose tolerance.

In Chapter VII is first described, in a normal material, the size of the profile surface of sella turcica on the roentgenogram determined according to the mm²-method of Haas. The border values have been statistically computed and reported for $\pm~2~\sigma$ and $\pm~2.5~\sigma$.

The mean values show good agreement with the values of *Haas*. During development the values of the both sexes follow each other up to approximately 8 years. After this age which is roughly coincident with that of the onset of prepuberty in the girls the values of the latter are higher (3—7 mm²), which also is the case for females in the age group 26—30 years (7—9 mm²).

In the second section of Chapter VII is described an investigation on the correlation between the size of the surface of sella turcica on the roentgenogram and the volume of the correspondent hypophysis in 27 non-endocrine autopsy cases. When the logarithm values of the hypophysis volumes are computed there is obtained a linear relationship to the sella turcica surface. The correlation coefficient $r=0.92\pm0.003$. As was to be expected the agreement is greatest for the lower values, while higher values for the sella turcica surface, notwithstanding the limited number of cases in this group, seem to correspond to hypophysis volumes with a considerably wider dispersion.

In the final section of this chapter is discussed the size of sella turcica in 350 obese children. Cases of diffuse obesity with 0—1 obese individual in the family, in which the obesity has debuted before age 6 and cases which according to reports have become obese in connection with a "non-cerebral" disease, have a definite skewness of the sella size towards low values.

The remaining groups of diffuse obesity show an accumulation of the majority of the values around the normal mean value with a scatter towards pathologically low as well as pathologically high sella values. This seems to suggest that the groups are not homogeneous.

Cases of gigantism and dwarfism show a trend towards high and towards low values, respectively, which may be explained by the different bodily proportions of the cases at the same chronological age.

The Fröhlich-like cases show a dispersion of the sella values which is wider than normal with a predominance of cases below the normal mean value. The classical picture of a large sella with a widened sella entrance was found in no case.

The skeletal development of the obese children has in 283 cases been referred to the normal standards of Lurie, Levy & Lurie (Chapter VIII).

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The untreated obese children, irrespective of the type of obesity show a skeletal age which with a mean variation of approximately \pm 2 years (= normal variation) clearly exceeds the chronologic age but is in good agreement with the height age. This shows that the skeletal age in obese children always should be assessed in relation to the height age.

Cases of gigantism and dwarfism included in the group diffuse obesity show retarded and accelerated skeletal development, respectively, in relationship to the height age. This seems to suggest that the skeletal maturation and the increment of stature are not quite parallel in these extreme cases.

In 16 cases a continuous thyroid treatment has been carried out for ≥ 1 year prior to the x-ray investigation of the skeleton. There does not appear to have been any resultant influence on the skeletal development in its relationship to the height age, irrespective of the duration of the treatment, which might have been-expected if a hypothyreosis had been present.

In 328 cases a follow-up examination has been done and on the results hereby obtained the investigation of the prognosis is based (Chapter IX).

The follow-up examination of 24 untreated cases of infantile obesity which on the average was carried out at the age of about $6^{1}/_{2}$ years, suggests that cases with >1 obese individual in the family more commonly are more obese than cases with 0—1 obese individual in the family. Generally, however, cases of infantile obesity may be considered as physiological extremes in which the obesity usually regresses during growth, and in which the incidence of cases of obesity in the family seems to afford a certain guidance in the evaluation of the further development of the weight.

The large group of obese children which at hospitalization on the average were taller than normal children of comparable ages were at the follow-up examination in adulthood (20—35 years) on the average shorter than the normal height for 20-year-olds. Giants and dwarfs seem also in adulthood to remain taller or shorter, respectively, than the normal height for 20-year-olds.

153 untreated cases of diffuse obesity and Fröhlich-like obesity which at the time of hospitalization were 7-13 years old, were followed up in ages 13—16, 16—20, or ≥ 20 . The boys showed a spontaneous successive decrease of the mean Rohrer-index value in the age groups 13-16 and 16-20, after this increasing in fairly good agreement with the normal increase of the group ≥ 20 years. In the girls the correspondent spontaneous changes of the mean Rohrer-index values occur in age group 13-16, but the rise occurs already in age group 16—20 and is in age group ≥ 20 considerably greater than that which normally takes place. In both sexes and especially in the female sex, the absolute figures for the mean Rohrer-index value in adulthood are considerably greater than the normal and approximately the same as the normal upper limit $(\pm 3\sigma)$. The prognosis in adulthood for untreated cases of obesity thus is rather variable and for obese girls considerably poorer than for the obese boys.

If the material according to the Rohrer-index value at age 7—13 is divided into a more obese and a less obese group it appears that the less obese children more commonly have a better prognosis than do the more obese children, the prospects seeming best for the less obese boys.

The material in adulthood is too small to bring out a difference between the two subdivisions of diffuse obesity, with 0—1 and > 1 obese individual in the family, respectively. In a larger obesity series this should be feasible, however, which is suggested, inter alia, by the difference in the distribution of the more obese and the less obese children in these two subdivisions of diffuse obesity, and hereby also in the result of the investigation of the heredity. The degree of obesity in adults as well as in children is influenced by the degree of their luxus consumption.

At follow-up investigations of the few Fröhlich-like cases there is on comparison with the cases of diffuse obesity not observed any difference in the prognosis for adulthood. The typical fat distribution seems to decrease or to assume a more diffuse distribution. The genital development seems, in the few cases observed, to take

place similar to the large group of obese children, thus probably somewhat earlier than the normal. No late puberal development is in any case demonstrable.

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The cases of pluriglandular obesity and cerebral obesity are too few in number to allow of a certain evaluation of the prognosis. These cases, however, seem to be especially resistant to therapy.

The treatment of the obesity material (Chapter X) has but incompletely been discussed as the number of cases treated over an adequate period of time and treated consistently is too small to allow of a certain opinion with regard to the efficacy of the measures of treatment followed. The treatment of the children treated during a shorter period (65 cases) has consisted of diet alone, thyroid alone, or of a combined diet and thyroid treatment. As was to be expected the treatment was most efficacious during the first months of treatment (diminution of overweight approximately 0.5 kg per week). The incidence of relapse was very great. Treatment exclusively with hypophyseal hormones, sex hormones, or chorionic gonadotropic hormone appears in the few cases observed in the present material to be without effect on the obesity.

In summing up it may with regard to obesity in children be said:

that weighty arguments speak for the common occurrence of a constitutional-heredofamilial factor in these children: thus, the difference in the degree of obesity and the point of time of the onset in the different incidence of obesity in the family; the results of the investigation on heredity; and in certain cases the characteristic size of the sella turcica on the roentgenogram; —

that the results obtained from the various investigations seem to show that a certain endocrine disturbance as etiologic to the obesity in children can not be established with the methods of investigation used: —

that the obese children during development show a physical and mental development which on the average is clearly in advance of that of normal children of comparable ages, this being manifest by the bodily proportions and a number of bodily factors, such as weight at birth, stature, time of onset of the prepuberal acceleration of growth, development of puberty, menarcheal age, basal metabolism, skeletal development and development of intelligence; —

that the results of the investigations on obese children with gigantism and dwarfism, respectively, should not be compared with the normal values for healthy children of comparable ages without taking consideration to the abnormal bodily proportions of the former; —

that cases of Fröhlich-like obesity (adiposogenital-like dystrophy) irrespective of the distribution of fat and an eventual temporary hypogenitalism do not exhibit anything which with certainty distinguishes them from the large group of obese children with diffuse non-characteristic obesity; —

that the prognosis in adult age for untreated cases is rather variable and dependent partly on the sex, partly on the degree of luxus consumption, and partly on the degree of the obesity in age 7—13, with the poorest prospects for the more obese girls and the best prospects for the less obese boys.

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A. LICHTENSTEIN

Kronprinsessan Lovisas Barnsjukhus, stockholm

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY, HELSINKI. CHIEF: PROF. A. YLPPÖ AND FROM THE DEPARTMENT OF PATHO

— ANATOMY OF THE UNIVERSITY, HELSINKI. CHIEF: PROF. A. SAXÉN

ON CHANGES IN DILATATION AND SIGNS OF ASPIRATION IN FETAL AND NEONATAL LUNGS

AN EXPERIMENTAL AND HISTOLOGICAL STUDY

BY

E. K. AHVENAINEN

ACTA PAEDIATRICA. VOL. XXXV. SUPPLEMENTUM III

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INTRODUCTION

At the suggestion of Professor A. Ylppö I began in 1941 my researches into the questions connected with the aeration of the lungs of newborn infants, using patho-anatomic methods of research. My work was interrupted by the war in June of that year, and I was able to resume it at the beginning of 1945. — It gives me great pleasure to express my deep gratitude to Professor A. Ylppö, for his valuable advice in the course of my work and his unfailing interest and encouragement.

My work has been mainly carried out at the Patho-Anatomic Institute of the University, Helsinki. I wish to express my most sincere thanks to the Head of the Institute, Professor A. Saxén, for his guidance, both in the choosing of methods and the estimation of the results. — My thanks are due to Professor U. UOTILA, for the valuable suggestions I have received from him.

I also wish to thank the assistant Doctors of the Institute for their valuable support — especially Dr. V. RITAMA, with whom I have had the repeated pleasure to discuss my work and to receive from him invaluable advice.

I am also indebted to Dr. C.-E. Räihä, especially for his help in questions of physiology.

The material has been partly collected at the I and II Women's Clinic of the University, Helsinki and at the Midwives' College. I whis to express my deep gratitude to the Chiefs of these institutions, Professor M. RAURAMO, Professor A. TURUNEN, and Professor A. APAJALAHTI.

I wish to thank the laboratory nurses who have prepared part of my sections, for their work executed with great care. My special thanks are due to Mrs. M. Hellman, who has carried out the main part of the fat stainings.

I am further indebted to all those of my colleagues at the Children's Clinic and the Patho-Anatomic Institute, who have in many ways assisted me in my work — and especially to Mr. S. Heino, for his tender care of the test animals.

I wish to express my best thanks to Mrs. E. Harden for her English translation of my Finnish original.

My researches have been aided by a scholarshipp from the Finnish Culture Fund (Suomen Kultturrirahasto) and from the Research Fund for Children's Diseases (Lastentautien Tutkimusrahasto).

Helsinki December 1947

E. K. Ahvenainen

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I Survey of Literature

1. Atelectasis

Jörg (1835) was the first to describe the persisting fetal condition of the lungs in infants, he called it Atelectasis or Pneumonatelectasis and determined it as win unvollkommener Ausdehnung oder Erweiterung der Lungen durch Luft». Jörg separated the atelectasis from other pulmonary changes in the newborn and proposed a new name to discriminate between it and such pathologic states as »hepatisatio, induratio, concretio etc.» According to Jörg, atelectasis was always a persistence of the intra-uterine state of the lungs and a secondary atelectasis was unknown to him. According to our conception of to-day, he attributed to atelectasis a much too great and independent a part. Before Jörg, as early as in the 17th century — a difference was observed between the lungs of the fetus and of an infant who had breathed (HARVEY) and the importance of this difference in regard to medical jurisprudence, where cases of infanticide were concerned, was also realised, by examining the capacity of the lung to float. (Schreyer, Bartholinus). Several publications described lungs of children who had breathed, found to be entirely or partly airless (Zeller, Schenck, Billard, Pieper). It is possible that some of them had atelectasis, but it was not clearly differentiated from other conditions and there was no plain conception as to its etiology. In any case, Jörg has the credit of having inventend the name Atelectasis and disconnected this state from other pulmonary diseases of the newborn. The discovery of secondary atelectasis is attributed to the Frenchman LEGENDRE. He examined older children (2 to 5 years) and found that their lungs were similar to fetal lungs. Contrary to Jörg's point of view, he was of the opinion that it was not a question of lungs having remained in the fetal state, but of lungs having reverted to it. He applied to this the name of *état fétal de poumon*. He considered that Jörg was wrong in his theory. In the first half of the 19th century Traube had drawn attention to atelectasis in adults and made experimental researches on atelectasis. Rufz had also made observations on a similar condition, without however differentiating it from the others. Weber (1851) found that atelectasis should not as a rule be considered as a cause of neonatal death. The cause of atelectasis should always be sought and it is often to be found in the central nervous system.

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Further, several observations show that at a post mortem examination also the lungs of such an infant can be airless who is known to have breathed and even cried after the delivery (NIKITIN, ORFILA, TAYLOR, WINTER, WOLF etc.). In order to explain these observations, the theory was propounded earlier that the lungs had never become expanded, and that even the crying had originated from air which had entered the bronchi. (v. Siebold, Maschka, Brefeld, FALK, PINCUS, HECKER, ERMAN), or that the lungs had become alelectatic in a secondary manner, in such a way that less air was drawn into the lungs at inspiration, than expelled from them at expiration (THOMAS, SCHRÖDER). — In his experiments on animals, Lich-THEIM (1879) was able to find such a region becoming atelectatic, where the bronchus conducting to it was occluded, he also noted that different kinds of gases escaped from this region with different rapidity, oxygen and carbon dioxide being quicker and nitrogen slower to disappear than air. On the basis of these experiments LICHTHEIM arrived at the conclusion that secondary atelectasis appears in the lungs through the resorption of air into the blood. By filling the lungs of newborn rabbits with oxygen, Ungar produced in them a secondary macroscopic airless condition. By poisoning the animals with curare, he obtained in his experiments a nearly complete airlessness of the lungs, as the young died slowly and respiration was arrested before the heart function stopped. HELLER (1914), plugging the bronchus of dogs, produced an atelectasis that began in the central parts of the lungs. The atelectasis was the slower to disappear after the removal of the obstruction the longer the obstruction was allowed to stay. Van Allen and Adams found, while experimenting with dogs that atelectasis was

born only when the breathing was strained, and that valvular obstruction produced it more rapidly than did total obstruction. They found, as Heller had done, that atelectasis was born centrifugally. According to their conclusions, *pent up bronchial air is probably lost from the lung by the blood stream absorption*. It is worthy of remark that Gairdner (1850) believed atelectasis to appear through the valvular obstructive effect of mucus in the bronchi. According to Hanson and Sjöstrand, the genesis of atelectasis is a complicated process, which they felt they could not explain on the basis of animal experiments.

In the above experiments, with the exception of Ungar's investigations, at electasis was caused by plugging the bronchus or by producing a pneumothorax, and therefore their application to the atelectasis found in the newborn is not quite plain straight away, as there may be other contributory factors than obstruction of the bronchi.

When the opinion became generally adopted that atelectasis could also be a secondary state in the lungs, the question arose whether the atelectatic regions often or nearly regularly (Thaysen) found in the lungs of the newborn, were of a congenital origin, or appeared in a secondary manner. Another question connected with this is how soon congenital atelectasis disappears. Jörg noticed already that lungs could be fully expanded »bald nach der Geburt» and there are several later observations on how the lungs of the newborn can be fully expanded, even if the infant had lived but shortly (STRASSMANN, G., YLPPÖ, FRITSCH). According to some investigators, on the other hand, there are congenital atelectatic regions in the lungs of infants several weeks old (Traisman, Rose). Ungar has maintained that when estimating different results, it must be taken into consideration that a different idea is obtained when examining the air-containing condition of the lungs of infants who had died in hospital, than in medico-legal cases of infanticide, as the former were often weak, whereas the latter might be strong infants who had died suddenly. Attemps were also made to establish by means of post-mortem material whether atelectasis was to be regarded as congenital or arisen in a secondary way. Mention has already been made of the divergent opinions of the 19th century. It can be said that later workers are divided into two opposite

groups. The one considers that lungs fully expand soon after delivery and the atelectasis is mainly or entirely secondary (Ungar, Ylppö, Loeschke, Klein, Seydel, Schmorl, Eckervogt, Kjerulf, Kathe, etc.), while according to the other, the expansion of the lungs is gradual process and atelectasis a persistence of the intrauterine condition. (Peiser, Canelli, Coryllos, Henderson, Rose, Potter, Siegel).

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Addison and How have examined the expansion of the lungs by means of animal experiments on dogs. They measured in a microscopic section the comparative amount of spaces in proportion to the lung tissue and arrived at the result that the expansion was gradual. In a section taken from the lungs of a newborn young after respiration had occurred, the expanded spaces were of a different size in different regions of the lungs. Older young had comparatively more expanded space than the younger animals. The same results were obtained by SNYDER and ROSENFELD in their experiments with rabbits. For a differentiation between primary and secondary atelectasis, endeavours were made to employ histologic methods of research. Before making a report on these researches, it seems advisable to give a short exposition of the fetal development of the lung, as it is essentially connected with the changes occurring at the moment of birth. — I omit the older researches, even extensive ones (e.g. FLINT) and confine myself to presenting the viewpoints of only a couple of investigators. It seems that Bender must be regarded as most important, his researches gave a consistent picture of the fetal development of the lungs, and his opinion seems to be practically universally and unanimously adopted (e.g. Heiss). Bender examined the fetal development of human lungs, beginning with an embryo of 9 weeks. At this stage the fetal lungs show an epithelial tubular system in a loose mesenchymal tissue. The ends of this tubular system, »Endknospen», are dilated and far from each other, separated by the said mesenchymal tissue. In these a nearly regular dichotomic division can be perceived. Bender called the »end-buds» pneumonomeres. The pneumonomeres have a large cavity, with a high prismatic epithelium. In the preterminal passage the epithelium is flatter than in the pneumonomeres, and the central parts have again a high epithelium.

The growth takes place solely under the influence of the dichotomic division in the pneumonomeres, but if disturbances occur in the evolution, this can lead to »Mehrlingsbildungen». Also in the usual dichotomic division one »Tochterknospe» is often larger than the other, i.e. asymmetric forms appear. The growth continues on the same principle, even if the number of asymmetric formations and »Mehrlingsbildungen» varies at different developmental stages. In the process of the development the capillaries increase and the mesenchyme decrease. An embryo 6 to 7 months old has a quite flat epithelium in the »Gangabschnitt», but a »helles kubischzylindrisches Epithel» in the pneumonomeres. In his researches on the late fetal stage Bender recurred to observations on the development of the lungs in the fetus of a cat, because it was difficult to observe the human fetus in its final stages of development, and as the lung of the cat greatly resembles the human lung, even if it is of a simpler structure. He was then able to establish that the sort of development described above continued until the end of the fetal life. In Bender's opinion, the growth of the lungs after birth continues in the same way as in the intra-uterine existence. In the pneumonomeres of the newborn a high epithelium is to be found, and they are incapable of gas metabolism. The s.c. respiratory epithelium is then to be found only in the end passages («Endgänge»), where the exchange of gases takes place.

According to Broman, the premature infant breathes with his bronchioli, and the alveoli are only born passively during extrauterine existence als Ausdehnung der betreffenden Bronchialzweigende an denjeningen Stellen, wo diese dünn geblieben sind.»

The changes in the layer of cells covering the inside of the alveoli at the onset of breathing as well as its character in the adult have been an object of research in the second half of the 19th century. While some investigators found the inside to be covered in adults by an uniform epithelium (Chrzonszcewsky, Colberg, Elenz), others considered it dissimilar (W. Addison, Donders, Eberth, Hertz, Arnold, Weber, Virchow) and a third group came to the conclusion that there was no epithelium on the inside of the alveoli (Th. Addison, Rayney, Zenker, Bakody, Henle,

MUNK). Those who had examined fetal lungs were generally of the opinion that at that stage there was epithelium in the alveol (WEBER, COLBERG), which therefore was there after birth, uniform or dissimilar. The viewpoints were mainly based upon the results of researches on animals, although some examinations of human lungs were also made. (WEBER, COLBERG, ARNOLD). The reason for the great changes in the human fetus at births was considered to lie in the onset of breathing (KÜTTNER). This change was further explained by surmising that its reason lay in the expansion of cells caused by expanding walls (JALAN DE LA CROIX); the cells were prepared for this expansion by the formation of mucus within them towards the end of the fetal condition (Colberg). In any case, the final result of the researches of the 19th century remained that breathing is of great importance for the changes in the epithelium (KOELLIKER). This opinion previled up to about the 1920-ies, and the same result was arrived at also by many workers during the first two decades of the present century. (Peiser, Marx, Addison and How, Strassmann, G.), although such a viewpoint was also expressed that the changes in the epithelium are gradual after the onset of breathing (RIDELLA).

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Ogawa (1920) has made a thorough examination of the development of the alveolar epithelium in the vertebrate and come to the conclusion that the change in the epithelium proceeds in accordance with the laws of evolution already in the fetal stage, and is not the result of the effect of breathing, although the cells become more flattened than before after the onset of respiration. The varied character assumed by the epithelium is also due to this evolution and is not the result of mechanical factors. Stewart (1923) came to the result on the basis of examinations of rats that a hydropic transformation and fatty metamorfosis take place in the epithelium, which makes it adaptable, while under the influence of the breathing movements it becomes more flattened and part of it comes off, which leaves the capillaries free. According to Stewart, the changes in the cells are probably also due to intra-uterine respiratory movements. Fauré-Fremiet (1920) believes that the changes of the alveolar epithelium are due to evolutions in the growing process and not to aerodynamic forces. Researches on fetal conditions have during these last decades led to the generally adopted opinion

that the epithelium, uniform in the early stages of development, gradually becomes varied (CLEMENTS, BARNARD and DAY, COOPER, Dogliotti, Siracusa etc.). This change is due to the dissimilar growth of the connective tissue and the epithelium (SEEMANN, (LARA) but the dehiscence of the epithelium can also be due to the development of capillaries (CLEMENTS). The epithelium assumes this character in the course of the 6th to 7th fetal month and the capillaries then get in touch with the alveolor lumen, after having been so far separated from them by the uniform epithelial layer and farther from the epithelium (CLARA, PALMER, BARNARD and DAY, Dogliotti). Also now there is a divergence of opinion as to whether the epithelium is retained after birth, or whether it disappears completely. (CLEMENTS, NORRIS and collaborators), in which case it would only have a canalisation function. (BARNARD and DAY). It is still a matter of dispute whether there is epithelium in the alveoli of the adults, and what kind of an epithelium, and whether its cells are of an epithelial or mesenchymal origin. I do not consider it necessary to go into the extensive literature dealing with this and the question of the origin of alveolar phagocytes, these being beyond the scope of my research. - The number of the cubic cells lining the fetal alveoli »end-buds» decreases toward the end of the fetal period and assertions have been made that the reciprocal relation among the number of cells of different shapes is some kind of a criterion for the viability of the child (Zeldes). Bensley and GROFF found by means of researches on rats that the changes in the epithelium take place just a little before birth and soon after. On the other hand, the structure of the lungs of the human fetus has been found to be the same in the 6th to 7th month as in the newborn (SIRACUSA), but it has also been maintained that it is possible to distinguish different phases in the adult alveoli (the static and the dynamic phase), when the relation between the epithelium of the walls and the capillaries is subjected to changes (COSTA). The opinion of Rose, that lungs are of a dual origin, with a separate appearance of alveoli and capillaries, and separate of bronchi, has not gained support. After the onset of respiration the high epithelium of the pneumonomeres disappears, according to Heiss, although he does not consider the postfetal evolution of the lungs as fully explained.

Differentiation between congenital and secondary atelectasis. — The determinations of congenital atelectasis in the textbooks and manuals are often very short, sometimes completely omitting the histologic picture. ZIEGLER (1890 and 1906) only mentions that if the respiration is defective, some regions remain airless, which is then a case of congenital atelectasis (»fötale Atelektase oder Apneumatosis»), Herxheimer (1910) determines atelectasis as »Zustand der Lunge, in welchem diese ganz oder in einzelnen Abschnitten luftleer ist, in welchem die Alveolen also zusammengesunken sind und die Alveolarwände einander anliegen.» Kaufmann's (1911) determination is as follows: ». die Alveolen eines Lungenabschnittes luftleer, sie haben keine polygonale Gestalt, sondern ihre Wände liegen aneinander. »Aschoff (1923) does not specify the histologic picture, but states that the lungs remain in the fetal unexpanded condition. Loeschke (1928) gives the following definition: »Als Atelektase bezeichnet man den Zustand, in dem sich die Lungen am Ende der Fötalzeit bezw. bei der Geburt vor dem ersten Eindringen von Luft befinden. Die angeborene Atelektase bedeutet also ein vollständiges Fehlen der Entfaltung der Lunge oder einzelner Teile derselben». Loeschke says however that there can be a lumen in the alveoli of the still-born, full of amniotic fluid, and therefore the »Entfaltung» of the lungs begins already to some extent before birth. Ribbert (1913) regards atelectasis as a complete airlessness of the lungs, and Hamperl's (1944) definition is equally short. Boyd (1934) presents a microscopic picture: »It resembles a secreting gland and is composed of gland-like spaces lined with cubical epithelium and separated by an abundant stroma». Beattle and Dickson (1943) as well as Bell (1944) determine atelectasis as a condition, where the lung is airless and the alveoli unexpanded. Bell says that the walls of the alveoli are »in close contact». Berg-STRAND determines atelectasis as a state, in which the air contents of the lung are reduced or have disappeared (»lungvävnadens lufthalt är minskad eller upphävd»), but he makes no separate mention of congenital atelectasis. The histologic difference between congenital and secondary atelectasis is not mentioned at all in the abovenamed textbooks.

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As to determinations of atelectasis made by individual workers or conceptions of the histologic characteristics of atelectasis, one

only finds in literature short references to them, or such references are entirely absent. Some investigators have observed that there are alveolar lumina in the lungs of still-born infants or animals (Appison and How, Snyder and Rosenfeld, Preuss) that can even be measured and is according to measurements made by ADDI-SON and How, 20-30 % of the entire area in dogs. Others admit that there are narrow spaces in a nearly compact tissue (MARX). BARNARD and DAY do not say anything about the lumen, but it is very distinct in the alveoli on the microphotograph of fetal lungs presented by them. WHITEHEAD and his collaborators came to the conclusion that the guinea-pig fetus did not have any alveolar lumen, but that it appeared only if the fetus aspirated or breathed - the lumen to be found in the alveoli of the human fetus they considered also to be due to aspiration. Even in such cases where congenital larynx atresia was present, expanded — even very much expanded — alveoli have been found. (Frankenberger, Kovacs). Artificially appearing changes have been considered the reason of the apparent spaces, which are only demonstrable in frozen but not in celloidin sections (Schönberg) — artificially produced spaces are however discernible from those due to inspiration of air (Orsos), and findings of small spaces in lungs with secondary atelectasis prove that the lung is not completely airless (FENGER). Orsos is of the opinion that the differentiation is easiest macroscopically - by examining whether there are on the surface air-containing alveoli and by pressing into them such air as might be found in the lung. Attempts have been made to achieve differential diagnosis by examining elastic fibers; it is then considered that a stronger staining or greater stretching of the fibers are characteristic for lungs that have breathed (BÖHMER, FOERSTER).

Peiser maintains that it is possible to determine, judging from the shape of the alveolar epithelial cells whether the infant had breathed or not, as according to him a cell is flattened by respiration and cannot reassume its cubical shape, even if the air escapes from the alveoli. Farber and Wilson have made thorough examinations of the histological difference in ininitial (congenital) and resorption (secondary) at electasis. They examined the question both experimentally and on the basis of human post mortem material

By distending the lungs of a still-born child in a Drinker respirator they were able to find that the alveolar lining cells changed from their cuboidal shape in the fetal state and became flattened, and their regular arrangement disappeared, so that when the air was lost again in consequence of secondary atelectasis, the distribution of the cells in the alveolar epithelium was uneven and the shape of the cells had lost its cubical form belonging to the fetal stage, having now become irregularly flat. They consider to have proved thereby that The cells lining the collapsed alveoli were flattened, irregular in position and unevenly spaced along slightly tortuous alveolar walls, as contrasted with the regular even spacing of cuboidal epithelial cells lining an alveolus which has never been expanded. In prematures they found masses of epithelial cells without alveolus formation.

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The post mortem material is an unrealiable basis for estimating the capacity to become air-containing in the lungs of the newborn. if only due to the circumstance that such infants who have died within the first few hours or days have breathed but weakly. Therefore attempts have been made to find out with the help of roentgenologic examinations how soon the lungs expand after birth. YLPPÖ ascertained that air was to be found everywhere as early as 5 minutes after birth, and 40 minutes after it the air contents had already increased. Dunham found atelectatic regions in 4 of the 6 cases he examined. According to Wasson's researches the lungs can be completely expanded as early as 5 minutes after birth, but in some cases atelectatic regions could be found even in two weeks old infants. These investigations showed that the rapidity with which the atelectasis disappeared had much to do with the character of the delivery. The results of other authors vary greatly (WEYMULLER and collaborators, Solis-Cohn and Druck, Dunham and AMICO, FARRELL), but it seems that some atelectasis is to be found several days after birth. The roentgenologic examination is however a rather crude method in this respect, and it fails to show up small atelectatic regions (YLPPÖ).

Attempts have been made to estimate the expanping capacity of the lungs by measuring the volume of respiration. The older researches are unreliable owing to technical difficulties (RECKLING- HAUSEN). Dohrn came to the conclusion that the expansion of the lungs was a gradual process. The improved methods of later years have yielded more reliable results. These investigations prove that the volume of breathing increases in the first days of neonatal life (Deming and Hanner, Deming and Washburn, Murphy and Thorpe). However, the inspiration when crying on the first day of life is superior or equal to that on the tenth day (Deming and Washburn) — this has already been pointed out by Ylppö, chiefly on the basis of clinical observations; he mentioned this in support of the rapidity of the expansion of the lungs, contrary to the results then obtained by measuring the volume of breathing.

On the Causes of Atelectasis. — The cause of congenital atelectasis was held to be the immaturity of the respiratory centre, (Peiper, CORYLLOS, POTTER) cerebral hemorrhages (STILL, BREFELD, KJER-ULF, DETRÉ and collaborators, POTTER) or malformations of the brain (POTTER) - but LEVINSON and SAPHIR did not find any relation between atelectasis and cerebral hemorrhages. In addition, atelectasis has been attributed to obstructions in the bronchi due to aspiration of the amniotic fluid in the intrauterine stage or in the delivery (SNYDER and ROSENFELD, CORYLLOS, BAUER, DEKKER-JONKER etc.), to the general weakness of the baby (GERHARDT), to cohesion of the moist surfaces of the air passages (Farber and WILSON, BAUER, CORYLLOS). Causes of the appearance of secondary atelectasis are partly the above-mentioned, but there are added to them a gradually progressing fatigue of the respiratory muscles (YLPPÖ), stasis due to a weak heart (YLPPÖ). There should also be considered obstructions of the bronchi by mucus due to inflammatory processes (Bartels, Gerhardt). As to atelectasis of the premature in particular, part of the above-mentioned factors have perhaps an even stronger effect in their case (muscular enfeeblement appears more easily than in healthier infants — cerebral hemorrhages are more common than in fullterm babies). In addition to these factors, it must be further considered, where prematures are concerned, that the pulmonary tissue itself is immature and therefore unable to expand (FARBER und WILSON). NORRIS et col. were of the opinion that the immaturity of the lungs is not in itself a cause of impeded breathing — the development of the lungs corresponding to the development as a whole.

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Potter says that even if the factor to which atelectasis is due is not always found, the latter is not enough to cause death. It must be added in this connection that a deficient function of the lungs may sometimes have a injurious effect on the functioning of the respiratory centre (Creutzfeld and Peiper), which makes the whole process considerably more complicated.

2. Intra-Uterine Breathing and Aspiration of the Amniotic Fluid

The first animal experiments, concerning fetal respiratory movements seem to have been made by Vesalius (1542). Several scientists observed the intra-uterine breathing movements of the fetus in animal experiments made in the course of the 17th and 18th centuries (Plater, Haller, Winslow); the reason of the respiratory movements was considered to lie in an interruption of the blood circulation between fetus and mother (WHYTT, DARWIN). Amniotic fluid substances were found in the respiratory passages of the fetus and the newborn (RÖDERER). SCHEEL (1798) supposed that the human fetus normally in- and expirates amniotic fluid, which remains in the lungs at birth and disappears from them through evaporation and resorption. Beclaro (1814) found in his experiments performed upon animals that the respiratory movements of the fetus became stronger if the circulation of the blood between it and the mother was purposely impeded. MAYER (1824) did not consider intra-uterine respiratory movements normal. When exploring the cause to which the onset of breathing was due, numerous experiments with animals were made and deliveries observed; in the early 19th century these researches formed the basis for observations on intra-uterine respiratory movement (Voltolini, Preyer, v. Franque, Kehrer, Lahs, Zweifel, v. Preuschen, Pflüger, HEINRICIUS, ENGSTRÖM), the opinions diverging both with regard to the cause of the onset of respiration and the intra-uterine respiratory movements. Schwartz (1858) considered the amniotic fluid to be found in the respiratory passages as a sign of intra-uterine asphyxia to which the aspiration of the amniotic fluid was due. Schultze

(1866, 1871) was of the opinion that the fetus can become asphyxial without aspiration and on the other hand, a transient asphyxia with aspirated amniotic fluid is possible, when the infant is born in good condition, with amniotic fluid in the respiratory passages, Küstner (1877) was the first to establish pneumonia as a consequence of intra-uterine aspiration. By means of animal experiments, it was possible to demonstrate that a coloured substance injected into the amniotic sac penetrated into the lungs of the fetus, but only in case of a disturbance of the placental circulation (Geyl, Preyer).

AHLFELD expressed his opinion in 1888 that the human fetus makes intra-uterine respiratory movements. It had already earlier been observed that there were repeated movements in the abdominal wall of a pregnant woman, and it was thought that these were sucking movements or singultus of the fetus, (MERMANN, REUBOLD). AHLFELD's viewpoint was based on his having observed rythmical movements in the abdominal wall of pregnant women that he could register and prove to be of the same type as the respiratory movements of the newborn. Weber observed these movements in 46 out of 54 pregnant women examined by him and they could be found beginning with the 32nd week of pregnancy. AHL-FELD's observations were not in general supported by his contemporaries. In his renewed experiments AHLFELD was able to demonstrate more clearly than before the existence of intra-uterine respiratory movements. Only a few authors agreed with Ahlfeld (Bütt-NER), while the majority maintained that they had never been able to observe such movements, or that they thought them to be something else, and not respiratory movements (FROMME, OLSHAUSEN, Runge). Rrifferscheid renewed Ahlfeld's experiments and came to the same conclusion. In order to throw light upon the question animal experiments have been carried on in the course of the last decades and it was observed that fetuses of different species of animals were not identical with regard to intra-uterine respiration (WINDLE and BARCROFT, SNYDER and ROSENFELD, BARCROFT, BAR-CROFT and BARRON, BONAR et col., SCHOCK, KLEMPERER). The different sensitivity of different animal species to the activation of intra-uterine respiratory movement has been explained as due to the dissimilar construction of the placenta; those whose placenta

is easily expelled, were thought to begin to breathe during the experiments in consequence of the coming away of the placenta, whereas those whose placenta is firmly adhering, do not begin to breathe, even if the uterine cavity is opened (Heinricius, Engström, Cohnstein and Zuntz). According to Barcroft's researches the age of the sheep fetus has its influence on how easily and due to what reasons it makes respiratory movements. Benecke demonstrated on guinea-pings, Snyder and Rosenfeld on cats and Wislocki on guinea-pigs and cats, that a colour substance injected into the amniotic cavity found its way into the lungs of the fetus whereas Windle and his collaborators came to the conclusion on the basis of examinations made by means of a roentgenography contrast medium, that guinea-pig fetuses did not as a rule aspirate amniotic fluid.

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In the course of the last decades and last years workers have attached importance to the intra-uterine respiratory movements and aspiration of the human fetus. American workers have made exact observations of the movements to be noticed in the abdominal wall of pregnant women, and partly compared them to the results obtained by experiment on aminals. Ahlfeld's old conception of the intra-uterine respiratory movements has gained new support (SNYDER and ROSENFELD, BONAR et col.). It was also observed that it is possible for the fetus to make respiratory movements already at a very early stage of fetal life (MINKOWSKI, WINDLE et col.). Dyroff was not able to discern any respiratory movements of the human fetus, when inserting a cystoscope into the amniotic cavity, although he saw the fetus making other movements. It has been possible to demonstrate that an x-ray-contrast medium injected into the amniotic fluid, passed into the lungs of the human fetus (ERHARDT, REIFFERSCHEID and SCHMIEMANN, DAVIS and POTTER). but this method of research has also yield negative results (MUGNAI and Ingiulla), or it was maintained that the said method of research was not conclusive with regard to intra-uterine respiration (WINDLE et col.) Aspiration was regarded as due to irritation of the respiratory centre caused by swallowed and absorbed contrast medium (PISCHINGER). SZENDI noticed that already a 3 months old human fetus aspirated colour substance injected intra-uterinally. Indian ink injected into the amniotic cavity did not pass into the

lungs of the human fetus (Pischinger). On the basis of theoretic consideration Walz arrived at the result that intra-uterine respiratory movements are an absolutely necessary condition for the maintenance of the fetal blood circulation, and that they regulate the latter. It seems as if his theory was quite conclusively overthrown (Dyroff, Schmitt). It cannot be considered that the idea of intra-uterine respiratory movements were universally adopted, as it has also been opposed (Eckstein and Rominger, Salmi). Yet Smith (1945) considers this opinion to have become "satisfactorily established".

· Mention has already been made of the elder viewpoints regarding aspiration of the amniotic fluid (RÖDERER, SCHEEL, SCHWARTZ, Schultze). Böhr found in his post mortem examinations of 57 stillborn or asphyxiated newborn infants that 41 of them had amniotic fluid substances in the lungs - according to macroscopic observations. Ahlfeld supposed that intra-uterine respiratory movement only caused the amniotic fluid to pass as far as the trachea, and Reifferscheid was of the opinion that respiratory movements took place with a closed larynx. Some later authors have adopted the point of view that in the course of intra-uterine life the amniotic fluid is only conveyed as far as the trachea or the mouth (BALTHAZARD and PIÈDELIÉVRE), whereas others maintain that if there are intra-uterine respiratory movements, they must also cause an aspiration of the amniotic fluid as far as the lung (FROMME, SCHMITT, PEIPER). This is connected with the old question as to whether the aspiration of the amniotic fluid is to be regarded as a sign of asphyxia in the fetus (Schwartz) or whether the amniotic fluid can be present in the alveoli also without asphyxia (SCHULTZE). Any special significance is not as a rule attributed to findings of small quantities of amniotic fluid (Hochheim, Johnson and Meyer, Loeschke, Weimann, Snyder and Rosenfeld, Bal-THAZARD and PIÈDELIÉVRE) - it is however considered that significant quantities of aspirated amniotic fluid are a sympton of asphyxia (NIPPE e.a.), while others feel that aspiration is always a sign of anoxia (WINDLE). Table 1 is meant to illustrate the frequency of occurence of amniotic fluid aspiration according to different authors. Their results cannot be compared forthwith, because their material is not similar, both with regard to the methods employed and the age at death of the subjects examined. Camerer has one of the most extensive materials, and according to him aspiration has occurred nearly to a hundred percent in infants who died under a week old. — No difference has generally been established as to the quantity of amniotic fluid in different lobes (Camerer, Hochheim).

Several authors consider that a strong aspiration is dangerous (Helwig, Szlavik, Shock, Camerer, Hochheim) and Franzmeyer is of the opinion that aspiration of the amniotic fluid is a complication mostly leading to death. Preyer thinks that the aspiration is rather an indicator of asphyxia than its cause.

The observations made in the researches mentioned in Table 1 are based in a microscopic examination of specimens taken from lungs. Different methods of staining have been proposed in order to demonstrate the presence of amniotic fluid in histologic preparations (RADTKE, STRASSMANN, F. etc.). Several authors have used fat staining in their researches (Hochheim, Camerer, Hook and Katz). FARBER and Sweet are of the opinion that hematoxylin and eosin staining makes the liquor amnii substances visible and that it is unnecessary to recur to any other methods. Of the amniotic fluid substances, cornified squamous epithelium cells are considered the most typical, and their presence most common together with fat. Meconium and lanugo hairs are met with more rarely (CAMERER, HINTNER). No conclusions can be made on the basis of the liquid part of amniotic fluid, because it does not fix owing to its low protein contents (Fraenkel and Weimann, F. Strassmann), or it occurs was a precipitate and so presents no distinctive picture (FARBER and SWEET) - yet WARWICK felt he could establish the presence of amniotic fluid in the lungs solely on the basis of the precipitate, and it was present without any firm particles in 25 % of his cases. Whitehead and his colleagues are of the opinion that the liquid substance found in the lungs is a transudate, and that there is in general no normal aspiration of the amniotic fluid, but to the contrary, a flow from the lungs into the liquor amnii. Ker-MAUNEE on the other hand considers that the mucus to be found in the respiratory passages is due to irritation of the mucous membranes and LEFF thinks that edema due to heart insufficiency is the reason of the circumstance that the lungs of the newborn seem

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TABLE 1

Presence of Liquor Amnii Substances in the Lungs According to

Post Mortem Material

Author	Age and number of cases	Presence of amniotic fluid
Hochheim	43, of whom 21 stillborn	In all
1903	and remainder newborn	
Thaysen	Under 3 days	In nearly all
1914	32 cases	
Hook	Under 14 days	In 43
1927	54 cases	
Hook and Katz	Under 17 days	Frequent
1928		
Loeschke	Stillborn	In all
1928		
Lauche	Under 2 days	In all cases in the respira-
1928	16 cases	tory passages, in 12 cases
		in the alveoli
Farber and Sweet	Under 6 weeks	88 %
1931	124 cases	
Szlavik	Under 9 days	In all
1931	35 cases	
Kaldor	Newborn	In 13
1933	17	
Murphy and Bauer	60 died under 24 hours age	In alveoli in 40 cases
1933	30 of them treated by res- pirator	
Franzmayer	Under 2 days	Cause of death in 31
1934	61 cases	(with complications)
Warwick	Under 2 weeks	73 %
1934	240 cases	
Camerer	Under 1 week	In 209
1938	212 cases	
Yamamura	24 cases of newborn and	In all fullterm infants, in 5
1939	stillborn	prematures out of 17

to be full with mucus — the amniotic fluid normally present in the trachea does not generate it, nor is aspiration its cause.

It is considered that aspiration of liquor amnii is significant for the development of the lungs. — The opinion has been expressed that aspirated amniotic fluid participates in producing changes in the alveolar epithelium, helping them to become flattened (SteWART). The fat to be met with in the cells of alveolar walls has also been considered to have its source in the amniotic fluid, but possibly to be also of some other origin (Hochheim). Snyder and Rosenfeld have come to the conclusion that liquor amnii constantly present in the alveoli, causes the apperance of the alveolar lumen in the course of fetal life.

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There are not many studies regarding the fate of aspirated aminiotic fluid in the alveoli. Of the older authors, Scheel was of the opinion that it evaporates and gets absorbed in the infant's lungs, Addison and How found in congenital atelectasis »Wanderzellen» in the alveoli of the lungs, whose task it was, according to their conception, to remove the »cellular debris», and the liquor annii would be rapidly absorbed. The fat was considered to disappear by resorption by way of the alveolar epithelium (Hook and KATZ) and the cellular particles disappear through the influence of phagocytosis and resorption (Hook). ERHARDT'S x-ray examinations proved that a contrast medium injected into the amniotic sac showed a shadow only 48 to 72 hours afters the injection, which ERHARDT explained as due to the circumstance that aspirated amniotic fluid was absorbed in the lungs, but the contrast medium remained, being incapable of absorption, and by means of repeated aspiration it was by and by concentrated so much that it gave a shadow, which it did not do in the concentration when it was in the amniotic sac. The same observations were made by Reifferscheid and SCHMIEMANN. CAMERER was of the opinion that already during the intrauterine stage the liquid parts of the amniotic fluid are rapidly absorbed, the fat is taken by the »Wanderzellen» and the capillary endothelial cells. The cellular particles of the liquor amnii are »der Alveolarwand angelegt» in infants a few days old, but CAMERER could not say anything as to their later fate. BENECKE is of the opinion, as a result of animal tests, that amniotic fluid is possibly absorbed by way of the lungs, although he was unable to demonstrate this conclusively in his experiments. — Particles of liquor amnii have been found in the lungs of prematures, even a couple of weeks old (Loeschke).

As already mentioned, CAMERER found the cellular particles of the amniotic fluid to be »der Wand angelegt». Chiefly American authors have drawn attention to the fact that liquor amnii sometimes forms membranes (FARBER and SWEET). Similar membrane formations are also to be found in the adult, mainly in connection with influenza (OPIE) but also due to other diseases - in children above all in pneumonia. (FARBER and WILSON) FARBER and SWEET called the membranes they found in the newborn »vernix membrane» or »hyaline membrane». FARBER and WILSON reported to have found them in 40 cases, and therefore the findings cannot be regarded as anything especially rare. Hochheim (1903) found already in two cases of the 43 newborn he examined in the alveoli a mass which is evidently identical with the membranes described later, and which he considered due to the aspiration of amniotic fluid in the newborn. Hochheim also found, like later authors (Farber et col., Hunt, Ahlström, Johnson and Meyer, STEINHARTER, HOOK and KATZ, BAAR, MACGREGOR,) that this mass was present only in infants who had breathed, and considered that it was due to the amniotic fluid being flattened against the alveolar walls. These membranes were found to be free from fatty material only in one case (Steinharter) of all reports on infants. They are stained in the same manner as hvaline (FARBER and WILSON etc.) and are free or nearly free from fibrin (FARBER and WILSON, AHL-STRÖM.) FARBER and WILSON produced experimentally similar membranes in animals and came to the conclusion that the chief factor effecting their appearance is an impeded - forced breathing, the result of which is the flattening of the contents of alveoli against the walls. According to their researches, these membranes are composed of disintegrating cells or necrotic tissues. Necroses have not been found in the alveolar walls of the newborn. Fat according to FARBER and Wilson is part of the membrane-forming substances, and not come from the blood.

Membranes were found in asphyxial newborn, the more pronounced, the more serious and prolonged the asphyxia (Farber and Sweet). Ahlström considers that the membranes can be a serious obstacle for the exchange of gases, and thereby a cause of death, especially in prematures.

Hochheim (1903) found a substance often present in the lungs of the newborn, blue when stained with hematoxylin in a frozen section, which has been named myelin (Virchow etc.). He

thought that this substance often appeared postmortally, but also intra vilam, as a result of aspiration of amniotic fluid. Myelin is formed of desquamating cells of the alveolar epithelium, where it is visible in a hematoxylin stained frozen section in Form schwarzblauer Tropfen und Schollen. Myelin was found by Hochhelm also in the lungs of older infants, where it could no longer be thought that the myelin formation was a result of aspiration.

Myelin is also found in the lungs of the adult, it is possibly a normal result of the excretion of the bronchial epithelium (Panizza, SCHMIDT), which are met with in expectorations as small granules (SCHULTZE). - According to KAWAMURA, myelin in the lungs of the newborn is mainly swohl sicher ein postmortales Produkts, whereas Aschoff considers that changes in the alveolar epithelium take place intravitally nunter dem Bilde von Myelinisation». Szla-VIK found myelin in the lungs of all the newborn he examined, nor was its quantity depending on the abundance of the aspirated amniotic fluid. He thinks that myelin present in the alveolar lumen shows that the alveoli were not aerated, and differentiates between congenital and secondary atelectasis on the basis of the presence of myelin. Weimann found that myelin appeared in decayed lungs of the newborn and in the cases of Hook and Katz myelin was more often found in those, where more time had elapsed between death and autopsy. It appears therefore that it is not possible to come to reliable conclusions on the basis of the presence of myelin in post mortem material.

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As may be noted from the above survey of literature, there are still some divergencies of opinion and questions in need of elucidation with regard to the researches on lungs of the newborn. I therefore feel that my investigation is justified.

II Material and Methods

The material has been collected at the I and II Women's Clinic of the University, Helsinki (N I and N II), at the Midwives College (K) and the Childrens Clinic of the University, Helsinki (L). Part of the autopsies has been carried out at the Patho-Anatomic Institute of the University, Helsinki (P). These were cases treated at the Childrens Clinic. With few exceptions, I have carried out the post mortem examinations myself, and made complete autopsies according to the method employed by the ZENKER school. I have tried to make the post mortem examination as soon as possible, and it has generally been carried out within less than 24 hours, in some cases in 1 to 2 hours after death. It must be admitted that some of my cases showed post-mortal changes that interfered with the estimation of my results, but by comparing to each other cases on which the outopsy was performed at different times after death, I feel it has been possible to estimate to a certain degree what changes are to be considered as appeared intra vitam. The lungs were removed in toto together with the organs of the throat and the thoracic cavity and placed whole into a 10 % solution of formaldehyde. After the fixation of the lungs in toto, pieces were dissected from each lobe, and in addition from the lingula. The pieces were subjected to fixation for a time of 24 hours in a 10 % solution of formaldehyde, after which they were embedded in paraffin, using chloroform as clearing medium.

The trachea was not ligatured before opening. It was not possible to fix the lungs in situ. It cannot be denied that this post mortem technique used by me can cause changes in the dilatation of the lungs, and it is even possible that the effect is not similar in all cases. In my experience, it is of no special significance to ligature the trachea of the newborn, because if one ligatures the trachea and unties it after the opening of the thoracic cavity, a hardly noticeable collapse of the lungs takes place, and in some cases no change can be noted. In the animal experiments, where a quantitative comparison of the size of the pulmonary lumina was made,

I have tied off the trachea.

Paraffin sections of 5 \u03c4 in thickness were stained with Weiger's hematoxylin and van Gieson, Delafield's hematoxylin and eosin. and orcein (1 per cent solution in 70 per cent alcohol with Hel) Part has in addition been stained by REGAUD's hematoxylin and Masson's acid fuchsin-aniline blue and by Harris' hematoxylin and MAYER's mucicarmine. In some cases the sections fixed in CAR-Noy's fluid were stained by Best's carmine, using Ehrlich's acid hematoxylin for staining the nuclei. In order to obtain a general idea, 30 μ , 60 μ and 120 μ thick paraffin sections were stained with DELAFIELD's hematoxylin and eosin. The frozen sections taken from the formalin fixed lungs, both upper and lower lobes, were stained with Romeis' colloidal sudan-orange or with scharlach-R (KRAJIAN'S modification), or both methods were used. For staining the nuclei in these sections Delafield's or Harris' hematoxylin were used. Part of the frozen sections was stained in addition by Nile blue sulphate and the Liebermann-Burchard-Schultze reaction was carried out.

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The frozen sections were also stained with Hoyer's thionine stain. In addition, such other staining methods as were considered necessary were applied in different cases. Weigert's hematoxylin and v. Gieson and Delafield's hematoxylin and eosin stainings were in as a rule sufficient to give a general picture, and I consider that other stainings were of great assistance only for analysing the alveolar contents. When staining fat, sudan was especially good to produce a intensive coloration, both with regard to fat revealed in the lumina and the inner fat in cells. On the other hand, the Nile blue sulphate produced a much weaker staining and did not by far reveal the relation of fat to the cells equally well as was the case in the sudan and scharlach-R sections.

I have tried to exclude from my material all macerated subjects and such who had had clearly visible inflammatory changes in the respiratory passages. I have considered such of my cases free from inflammation, where my sections did not show accumulations of inflammatory cells, either in the lumina or in the walls. The presence of a few granulocytes was not considered sufficient to exclude the case. Partly due to the reason that it was difficult to collect enough material free from inflammation, I have been constrained to include some such cases where there were some restricted inflammatory changes. Moreover, all such cases that were affected with syphilis, either found out clinically or by post mortem examinations, have been omitted. - Hepatic changes may be regarded as some kind of a criterion of possible syphilitic changes in the infant, because they appear in abt. 70 to 80 percent of congenital syphilis cases (Thomson). Therefore pieces taken from the liver have been examined microscopically in order to ascertain the microscopic changes.

I have considered the age of one month as the upper age limit of the cases in my material. The downward limit was set at 600 gm weight at birth. The majority of the cases are under 10 days old. For the sake of comparison I have also examined older infants. The material comprises in all 95 cases, from stillborn up to half a year old infants. The division of the material into premature and fullterm infants is revealed by the discussion of the cases. According to the now generally adopted determination of YLPPÖ, I have regarded as premature such habies as weighed at birth < 2.500 gm. In conformity with the opinion proposed of late, I have placed into a separate group immature babies who had a birth weight < 1.250 gm (v. Numers, Ylppö, Henderson).*)

In addition to the above material I have also had at my disposal the observations I made at post mortem examinations of infants of different age, as well as microscopic preparations from them, stained with Weigert's hematoxylin and van Gieson, or with

DELAFIELD's hematoxylin and eosin.

The clinical data regarding the cases was obtained from the case or delivery histories. Some infants treated at the Childrens Clinic I have been able to observe from a few hours old until their death.

To complete my post mortem material, I have also carried out several animal experiments. This material is dealt with in a dif-

ferent chapter.

To determine the shape and staining of the liquor amnii substances, films were made from amniotic fluid taken from an undamaged amniotic sac; these films were stained by Weigert's hematoxylin and van Gieson and by Delafield's hematoxylin and eosin, as well as by Romeis' colloidal sudan-orange. In the films thus stained it was possible to distinguish large nuclear cells as well as squamae without nuclei. These presented a similar appearance as the squamae and cells in bits of skin taken from newborn infants. There were also some smears that did not contain more than some single cell and squama, and in addition to them only a precipitate. Even if it appears clear on the basis of the above that amniotic fluid can chiefly appear as a precipitate in the sections, yet I have not regarded the presence of this substance to be a conclusive proof of the presence of amniotic fluid, unless there were other unmistakable reasons for such a supposition.

Calculations were made using the net ocular both on the basis of human post mortem and animal material, how high was the percentage of the area free from parenchyma in both materials, as compared to the total area. The net ocular had 340 squares, and a 300-

^{*)} I am using below "premature" to designate as a group denomination both premature and immature babies, unless it is clear from the context that only that group is meant, whose birth weight is 1250—2499 gm.

magnification was used. When calculating, the areas were chosen in such a way that they were not taken into consideration if they showed lumina that might be interpreted as bronchi or bronchioli, but the section was moved until they disappeared from the field. In this way, at least 15 fields were counted in each section, but if some items showed considerable differences more fields were counted, and it was then attempted to count different areas separately. By using this method of calculation one does not obtain the pactuals size of the lumina, the result only showing their relative proportion. Notwithstanding this, the methods allows of a better comparison of the different cases to each other, than by only measuring with the eye.

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III Experimental Investigations

Material and Methods. — The experiments were made on kittens, of which I had 10 litter at my disposal. For some a cesarean section was performed at the end of the estimated pregnancy, some were born spontaneosly. When performing the cesarean section, the cat was anesthetised with choloroform, subsequent to having received morphine 0,04—0,06 subcutaneously. The kittens were weighed immediately after birth. In all these cases, with the exception of the first-born litter, the trachea was tied off before opening the thoracic cavity. After an examination of the lungs in situ, the whole animal was immersed in a fixative solution; in the majority of the tests a 10 % solution of formaldehyde was used as such, and in some cases susa solution (Litters No. 3, 4).

Some hours later the organs of the thoracic cavity were removed and immersed whole in the fixative, the trachea still being tied up. As soon as it was seen that the fixation had taken place, pieces were taken from both sides, both from the upper and lower part, always endeavouring with the utmost possible precision to take pieces from corresponding places. The pieces were embedded in paraffin in the usual way, employing chloroform as clearing medium. $5\,\mu$ thick sections were cut and stained with Weigert's hematoxylin and van Gieson and Delafield's haematoxylin and eosin as well as orcein. Some serial sections were made and stained in the above way. In addition, some $30\,\mu$, $60\,\mu$ and $120\,\mu$ thick sections were cut and stained with Delafield's hematoxylin and eosin.

In the cases of the cesarean sections as well as in some spontaneous deliveries it was possible to exactly determine the time of birth, but in some cases it could be established only with the precision of hours. These circumstances will be elucidated in the tables. In order to provoke the appearance of secondary atelectasis the following method was used: the kitten was allowed to breathe oxygen for a time of about 10 minutes. After that curare was administered to it (intraperitoneally 0,1—0,5 c.c. of a 1 percent solution), and the animal was left to inhale oxygen until it died. In these experiments respiratory activity ceased before the heart stopped.

The latter's function became gradually slower. These kittens were treated after death in the same way as explained above. The lumen ration in 5 μ thick sections was calculated according to the method set forth on p. 29. The results of these proceedings are illustrated by tables 2, 3, 4.

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Observations

Lungs with Congenital Atelectasis. — These researches were made by studying the lungs of 5 kittens in all. Three of them were killed intra-uterinally, without ever having been allowed to inhale air (Kittens 1/II, 3/II and 11/I), one was made to inhale a little air (7/III) and one kitten died of sintra-uterine asphyxias in such a way that it was placed into formalin enclosed by the uterus (10/II). The three first ones show a more or less equal expansion (see table 2), although it is different in different lobes. This cannot be measured by the eye, but is only revealed by counting.

TABLE 2

Kittens Killed in Utero

No. of kitten	Lumen ratio (%)										
	1	11	III	IV	Average						
1/II	45	46	45	37	43						
3/11	44	49	43	52	47						
7/111	60	63	53	61	59						
11/I	50	43	36	41	43						
10/II	52	60	72	62	62						

The numbers signify: I upper part of right lung, II lower part of right lung, III upper part of left lung, IV lower part of left lung.

The structure of the lungs of kitten 11/I was as follows: Macroscopically: the lung is of a light red colour, with a soft consistence, most like to that of a gland. The surface of the lung is of an even colour. Microscopically: all the lobes present a similar picture. (Fig. 1) Lumina are clearly discernible everywhere, the tissue looks *nice* and regular. The walls are winding, but the walls in general are not too thick; they make a thicker impression than *sin reality*, owing to their strongly intricate course. The elastic fibres are wind-

ing, "flabby". In the thin places the walls only have a thin fibre, or there is a single cell adhering, or a capillary springs up from it. The epithelial cells *) lining the walls can be clearly distinguished from the other parts of the walls, and hang sometimes like grapes or berries from their thin central parts. There are one or two cells - very seldom more (3-4) in one place. Their nucleus is of the size of a erythrocyte, round or elliptic. Protoplasma forms a smaller part of the cell than the nucleus. The shape of the cells varies from low prismatic to high prismatic. So e.g. there is a wall near the pleura (under it) that has three highprismatic cells, then a capillary and again two isolated cells with a capillary between them — these cells are isoprismatic. The same variation in the shape of the cells down to the lowprismatic form is seen in different places of the section. In addition to epithelial cells, the walls have capillaries whose endothelial cells have narrow fusiform nuclei. The share of the capillaries is about half the wall. They do not have any unbroken arrangement in the walls on larger areas than what corresponds to the width of 2-3 epithelial cells. In addition to them, the central parts of the walls have cells with fusiform nuclei. In the lumen isolated epithelial cells are demonstrable, which are vaculated. There is also some angular shape without a nucleus that stains a light yellow with Wiegert's hematoxylin and van Gieson, and light red with Delafield's hematoxylin and eosin. Some erythrocytes are seen, and sometimes a precipitate. The lumen is mainly empty. Two nuclei are seen sometimes in the cells situated in the lumen. Kitten 1/II presents a practically similar picture, but the cells can be better distinguished from each other. Kitten 3/II is also similar.

These cases show here and there small areas that only consist of cells — the wall appears thicker, but it is then a place where the lumen has been cut tangentially, so that the »bottom» or the »ceiling» become visible. This impression is gained when examining 30 μ and 60 μ thick sections. Such forms where the lumen is encircled by an unbroken regular ring of cells, are not to be found in the sections.

^{*)} I am using here and below the name of epithelial cells when referring to cells covering the walls for greater clearness, meaning the cells lining the walls and morphologically resembling epithelial cells.

The lungs of the kitten 10/II asphyxiated intra-uterinally are macroscopically unmistakably larger than those of the preceding cases, and according to calculations made on the basis of microscopic sections, the lumina occypy a visibly greater part than above. Some places show variations within about similar limits as in the forementioned cases. The microscopic examinations also show at once a much greater extension of the lumina, but in other respects the microscopic picture of the lungs does not differ much from the above. (Fig. 2) The walls are straighter, but have no proper »tension». The cells seem to lie at greater distances from each other. Their shapes are identical with those described above. No visible difference can be established in the relation of the epithelial cells to the connective tissue. The number and blood-contain of capillaries are about the same as in other cases of intra-uterine death. This being so, there is no evident difference but in the size of the lumina. The picture as a whole reminds of other cases of intra-uterine death. and diverges from the microscopic picture of lungs that have breathed to such an extent, that it must be placed into the preceding group, in spite of the noticeably larger lumina. The alveolar region does not have any contents worth mentioning, to the contrary, there is less of it than in other cases of intra-uterine death, but instead there are in several bronchi quite a number of the angular formations described above, staining a light colour (amniotic fluid),

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The lumina are of about the same extension in the case which was allowed to breathe some air through the torn trachea (kitten 7/III, Fig 3). In this case the calculations did not show the difference between the expansion in different lobes to be greater than in lungs that had not breathed, but when examining microscopically tissue sections, it is seen that some sections have areas of a different character. Here the walls are somewhat more »tense» than in lungs with congenital atelectasis, the difference being yet very little—in point of fact so small that it would be impossible with certitude to transfer it into the air-breathed group. The shape and arrangement of the cells and their relation to the other parts of the walls do not differ greatly from those described above. In some places the cells are not distinguishable so clearly, giving the impression of being pressed against the walls. These latter appear somewhat thicker than in the lungs of other cases with congenital atelectasis. With

regard to its weight, this kitten was somewhat more removed from a fullterm animal than those dealt with above.

Acrated Lungs. — My material comprises in all 29 kittens who had breathed air. Attempts were made to affect 10 of them with secondary atelectasi; — I am dealing later with these cases. Nineteen kittens were allowed to breathe freely. They were killed at different ages — at the utmost two days old, and one of them died.

Aerated lungs are already macroscopically easily distinguishable from the lungs of those who had died intra-uterinally, as described above. They are unmistakably more expanded, of a light colour, and showing on the surface transparent aircontaining lumina. The microscopic picture (Fig. 4, 5, 6, 7) is also quite different from the one presented by the animals described above, who had died intrauterinally: the walls are straight, "tense" - they look thinner and the number of capillaries is smaller (in other words, the capillaries contain less blood) than in animals who had died in utero. The elastic fibres are tense. In addition, it can be seen in thin sections (5 μ) as a difference from animals with intra-uterine death, that the contours of the lumina are straighter - the irregularities that are due to the epithelial cells and capillaries rising from the walls, are absent in these sections. Epithelial cells are few, and clearly distinguishable only in the corners. In these places and in thick sections there are alveolar lining cells with a shape that is strongly reminiscent of the cell shapes seen in the lungs of animals who had died in utero. I have been unable to find any alterations in the forms of the cells in these sections, on the basis of which it would be possible to discriminate between a lung that has breathed and a lung of an animal who has died intra-uterinally.

I do not feel I can, on the basis of the staining methods employed by me, go into the widely discussed question as to whether respiration causes changes to appear in the cells of the alveolar lining, and as to what is the cause of the difference between the alveolar walls of a fullterm fetus and a newborn animal who has breathed. The purpose of my study has been in the first place to clear up the difference between the pulmonary structure of lungs with congenital and secondary atelectasis. As this difference, according to my opinion, is better illustrated by the general pulmonary picture than by

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Lungs with Secondary Atelectasis. — As already mentioned above, I have attempted in ten cases in all to provoke secondary atelectasis in the lungs of newborn kittens. In some of them it was possible to render the lungs macroscopically entirely airless. Microscopically spaces could be found also in sections made from such lungs — and upon counting the ratio of spaces appearing in the whole area of the section, it was found that it was more than 10 % of the area, although there were places in the section that were entirely devoid of lumina.

The lumina of the lungs that appeared at electatic on the surface were on an average unmistakable smaller than in the lungs of animals where respiration had taken place and that were killed suddenly. It is justified to consider these lungs at least partially at electatic, and on the basis of the picture presented by them, to estimate the difference between congenital and secondary at electasis of the lungs.

As already said, the sections showed areas where no lumina could be distinguished at all. Such areas can therefore be regarded as completely atelectatic. They are unmistakably of a different construction than the lungs of animals killed in utero, already on the basis of the general picture presented by the section (Fig. 8). The tissue is compact, irregular, and cannot easily be recognised as lung tissue. There are variations in the form of the cells, but it is impossible to establish any fundamental difference as compared to the lungs of animals killed intrauterinally. In these places it is difficult or impossible to distinguish the epithelial cells from other cells of the wall (see Fig 9). There are better possibilities to study the structure of the walls in those places where there is a small slitlike lumen (Fig. 10). The walls are thicker in comparison to those in the lungs of fetuses killed in utero. The whole structure is coarser, the lumina do not have as many partitions as in the lungs of these latter. The epithelial cells are not as clearly distinguishable as those rising isolated in the lumen, but they are »pressed» against each

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other, forming in this way together with the capillaries a uniform lining of the walls. When studying thick sections, it is seen that the lumina look slitlike, in contradistinction to those of a regular round shape in the animals killed intra-uterinally. The corresponding places of the sections taken from the lungs of kittens of the same litter show a great number of small, round or oval lumina in the lungs of animals who died in utero, whereas in lungs affected with secondary at electasis the lumina are slit-like and much fewer in number. I do not feel that it is possible to distinguish these lungs from those of animals killed in utero on the basis of the forms of epithelial cells.

Attempts were made to affect the kitten 7/IV with secondary atelectasis at the age of 4 hours. The animal was premature, weight at birth being 75 gm. Its breathing had been weak and rattling the whole time. The conditions under which the experiment was made and its course were similar to the other cases. The lungs did not become completely atelectatic, but it was possible to distinguish macroscopically areas that were unmistakably air-containing. The left lung presented macroscopically and microscopically an appearance of congenital atelectasis and lumina were clearly seen everywhere. A section taken from the right lung showed some lumina with arched »tense» walls, where the cells could not be seen clearly. The experiment speaks on behalf of the supposition that the lung, in order to become atelectatic in a secondary manner, must first be aerated — i.e. that the alveoli do not collapse unless some air had entered them first. In the animals of the same litter that had a longer life (7/I and 7/II) atelectasis could be macroscopically determined everywhere in the lungs, and the shape of their walls and lumina was microscopically different from congenital atelectasis. In the lively kitten (5/III), which was subjected to the oxygen-curare treatment when 2 hours old, the lungs became macroscopically airless and the structure differed microscopically from congenital atelectasis. The lumina were comparatively larger than in the kittens 7/I, 7/II and 4/II, which were older when subjected to treatment.

Discussion

As stated at the beginning of the chapter, the lumen ratio in the lungs was counted. The results of these counts are illustrated by tables 2, 3, 4.

TABLE 3

Kittens in whom Respiration had Occured

No. of kitten	Age.	Lumen ratio (%)									
	nge.	1	11	111	IV	Average					
1/III	2½ hours	45	53	30	40	42					
1/IV	54 hours	56	40	57	61	52					
4/111	1 1/2 days	53	61	50	58	56					
5/1	25 hours	52	50	52	47	50					
5/11	53 hours	44	54	47	42	47					
5/IV	2 hours	57	53	59	50	55					
6/I	1 hour	46	43	44	42	44					
6/II	20 min.	62	. 53	70	53	60					
8/I	2 hours	66	66	. 58	56	62					
8/11	42 ,,	77	77	69	77	75					
8/IV	20 ,,	57	57	51	46	53					
9/I	2 days	54	45	56	45	50					
9/11	2 ,,	35	54	46	72	52					
9/111	2 ,,	49	69	57	83	65					
9/IV	2 ,,	75	81	42	41	60					
11/II	45 min.	91	79	85	73	82					
11/III	10 ,,	47	49	50	58	51					
11/IV	10 ,,	74	54	75	55	65					

The numbers signify: I upper part of right lung, II lower part of right lung,
III upper part of left lung, IV lower part of left lung.

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In the lungs of the animals killed intra-uterinally the lumina in the different cases belonged to about the same class of size in the kittens 1/II, 3/II and 11/I. These animals were killed in the same way by squeezing the trachea while the fetus was within the amniotic sac. They were not seen to breathe and neither macroscopically nor microscopically could any areas be found that might be considered having become aerated. In this respect the lungs are congenitally atelectatic. The fetuses did not, while they were visible, aspirate any amniotic fluid in the uterus. The other animals of the same litter did not begin breathing immediately after birth, but remained in a state of apnoea for a few minutes. In each case the mother had received morphine and been anesthetised with chloroform, which may have partly been the reason why the kittens were

TABLE 4

Kittens Treated with Curare and Oxygen

No. of kitten	Age.		(%)			
		I	II	111	IV	29 39*) 18 32
1/V	49 hours	26	31	24	34	29
4/I	1 ½ days	41	47	31	39	39*)
4/II	1 1/2 ,,	17	20	19	17	18
5/III	3 h.45min.	30	31	32	34	32
7/I	77 hours	24	22	21	25	23
7/11	23 ,,	28	18	. 14	18	20
7/IV	6 h.20min.	40	37	43	43	41

The numbers signify: I upper part of right lung, II lower part of right lung,
III upper part of left lung, IV lower part of left lung.

not active. It can therefore be said that there evidently had not been any extension of the lumina in the lungs after the cesarean section was begun. It is impossible to say whether the fetuses had made intra-uterine respiratory movements when the anesthetic first took effect, and whether this may have modified the »normal» intra-uterine state of their lungs. I feel however it can be indisputable affirmed that the lungs were congenitally atelectatic in all these cases, according to the general interpretation of this concept. Even if the microscopic picture of the lungs does not in every way fulfil all those demands which have been laid down for congenital atelectasis of the lungs. (See p. 14).

Fetus 10/II suffocated in utero without ever having breathed air. Its lungs did not otherwise differ from those described above, but for their unmistakably larger size, even macroscopically. Microscopically their lumina were quite evidently more extended than in the three previous fetuses, and when counting the ratio of the lumina, it was possible to ascertain that the ratio was much higher than for the others. If this case is set apart from the others without considering it any more as congenitally atelectatic, one arrives at the result that the lungs of a fetus that had died intra-uterinally

^{*)} only curare

and not inhaled air, are not necessarily congenitally atelectatic. It is evident that when the fetus dies in utero, factors often occur that constrain it to aspirate amniotic fluid, even in considerable amounts. If they are removed from the group of congenital atelectasis, this may often cause still greater confusion with regard to some individual cases, as to whether a certain case should be considered congenitally atelectatic or not. The easiest course therefore would be to regard such cases also as congenitally atelectatic, irrespective of the extension of the lumina. This latter should then be left out of the determination of congenital atelectasis (in so far as it is wanted to make this determination on the basis of the histologic picture). I shall revert to this question with regard to the human fetus in the chapter dealing with human post mortem material.

In the lungs of such kittens who were allowed to breathe air but were killed suddenly, the size of the lumina was subject to great variations in individual cases. There are also sometimes greater variations in the different lobes of the same case than what is seen in different places of congenitally atelectatic lungs. These variations in size are noticeable also in such cases where the lungs appear fully aerated macroscopically, nor are there any atelectatic areas to be found microscopically. The lumen ratio in the lungs of the kittens belonging to the same litter but killed in different ways (kittens 9/I-9/IV) varied considerably. If it is taken into consideration that already in lungs with congenital atelectasis the lumen extension can be 40--60 per cent of the whole area in microscopic sections, it is evident that it is impossible to determine the aeration of the lungs only on the basis of the size of the lumina - or at least, it is impossible to say whether some area is air-containing or not. It also appears evident that the different kittens cannot be compared to each other on the basis of such calculations. A comparison of the lumen sizes of kittens 8/I-8/IV speaks for the supposition that the lumen ratio grows in the course of the first 24 hours. Yet the material is so small that it does not allow of any conclusions if the differences are not more considerable than those illustrated by the tables. A better idea of the aeration of the lungs than a simple counting of the size of the lumina, is a microscopic study as to whether the lungs show any atelectatic areas. Having made a discrimination on the above principles between congenitally

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There were great variations in the extension of the lumina in lungs affected with secondary atelectasis by means of oxygen inhalation and curare. Not a single time was it possible to achieve a complete absence of lumina in the whole area of the lung. While the lung appeared macroscopically airless, tough, of a dark grevishred colour, spaces were clearly seen in the microscopic section. The lumen ratio averaged about 20 % in these cases. According to these counts, the lumen was unmistakably less extended than in the lungs with congenital atelectasis. Even if there were completely airless areas in the lungs whit secondary atelectasis, and one can therefore say that complete atelectasis is possible, -- yet it cannot be denied that in these cases such areas are also atelectatic where narrow spaces are found in the tissue. The borderline between atelectatic and non-atelectatic is not clearly defined here. I do not find it indicated, or even possible, on the basis of this material comprising only newborn kittens and secondary atelectasis originated only in one way, — to go into the question of atelectasis appearing in a secondary manner, or to attempt a general determination of it. In such cases that were airless (atelectatic) macroscopically, the extension of the lumina was 20-30 per cent of the section area. The lumen ratio clearly surpassed that percentage in the cases that showed macroscopically aerated areas (Kitten 4/I). — It is possible that the lumen ratio is different in different species of animals, therefore conclusions can be made on the basis of the above only in so far as newborn kittens are concerned.

Conclusions

Kittens that are not allowed to breathe air and whose lungs are macroscopically airless, show unmistakable lumina over the whole pulmonary area, their ratio amounting to about half of the latter. If the kitten had strongly aspirated intra-uterinally, the lumina were considerably more extended, but the lung still retained a construction reminding of congenital atelectasis.

At the onset of respiration changes take place in the lungs of the kittens, not only in the shape or extension of the lumina, but the structure of the walls also alters. It is not considered possible in this paper to differentiate on the basis of the forms of the cells between initial (congenital) and secondary at electasis.

It is possible to distinguish secondary at electasis in kittens from the fetal condition of the lungs, as well as on the basis of macroscopic and microscopic characteristics. In lungs affected with secondary at electasis the lumina are smaller than in the airless lungs of a kitten dead at the time of birth. Microscopically a difference is seen both in the shape of the lumina and the position of the cells on the walls.

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IV Human Post Mortem Investigations

1. Congenital Atelectasis and Aeration of the Lungs

Fullterm Infants

Stillborn and Asphyxiated who did not Resuscitate. Congenital Atelectasis

There were 14 stillborn in ants according to the delivery histories. It cannot be considered a priori that the lungs of stillborn infants are the same as in the fetal state. I.e., they are not a suitable starting-point for a research as a type of lung where no respiration has occurred. There are numerous observations as to how stillborn babies — even fetuses taken out of undamaged amniotic sacs — both macroscopically and microscopically show air-containing areas in their lungs (Lados, Kathe, Hofmeier, Dürig, Raestrup, Meixner, Schönberg, Strassmann, Hecker, Wille).

Of the stillborn babies of my material one died during pregnancy and the others in the course of the delivery. Of those who died during delivery five were such (cases no. N 2143/I/44, N 906/I/46 A, K 719/45, K 1811/45 and K 643/46), in whose lungs it was possible to find already macroscopically air-containing areas on the surface of the lungs, differing from the pulmonary tissue elsewhere. Nine others were more or less similar to each other. Their lungs were tough, resembling glands in their consistence, the surface was smooth, regular, the colour varying between greyisch-red and greyish-purple. The lungs sank in formalin.

The only case of my material who died in the course of pregnancy (N 626/I/45) had small, greyishpurple lungs. The following was found by means of a microscopic examination of them: The epithelial lining of the bronchi and bronchioli had come off in small patches everywhere and filled their lumina. The main

part of the tissue of the alveolar tree was formed by engorged capillaries. The endothelial cells in the capillaries were clearly visible, their nuclei were crescentshaped, well stained. There were but few cells in the alveolar epithelium — they were generally detached in the lumen. Only some cells adhered to the walls. Their shape was isoprismatic, sometimes somewhat higher, sometimes somewhat lower. The form was often irregular and the protoplasma indistinctly visible. The nucleus was round or elliptic, well stained. The cells in the connective tissue of the walls were well preserved. The shape of the nuclei in the cells of the connective tissue was fusiform, the nucleus often arched, its length about 3—4 times larger than its thickness. Long and narrow nuclei were nowhere visible in the cells of the connective tissue.

The case was not a good one, in so far as the postmortal changes were already far developed, but such changes are so rapid in babies who die during pregnancy, that they are already present at birth. The post-mortal changes were even more advanced in other infants dead during pregnancy whom I have examined, and their tissue structure was entirely blurred.

In case N 2246/II/45 there was a striking engorgement of the blood vessels in the histologic section. There was a clear preponderance of capillaries in the walls, and also touching the lumen nearly exclusively engorged capillaries. Their endothelial cells had crescentshaped or fusiform nuclei. The walls ran a tortuous course and the capillaries bulged out into the lumen. The alveolar epithelial cells were usually single in each place, but in some places 2-3 close to each other. They were iso- or lowprismatic, the nucleus was round and well stained, lying in the centre of the cell or somewhat basally. Protoplasma was slightly stained, taking up half the cell at the utmost. Sometimes the cells in the capillaries can misleadingly resemble epithelial cells, but it is possible to make the distinction on the basis of the shape and situation of the cells. Cells resembling those of the alveolar epithelium were found detached in the lumen. In such cases their protoplasma was granulated -- some cells were clearly disintegrating. The nuclei in the cells of the connective tissue of the walls were fusiform, their length surpassing their thickness 2-4 times. The bronchial epithelium was well preserved and stained strongly. Thus, there are no essential differences between this case

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Micro descr and those who had died in utero, the differences having probably been produced by the abovementioned post-mortal changes.

The highest lumen ratio was found in cases N 2686/II/45 and N 810/II/45 (see table 5). Their microscopic picture does not greatly differ from the preceding. The lumina appeared here more extended and the walls thinner than above. The amount of blood in the capillaries was evidently less than in those with smaller lumina. There were also in these cases clearly discernible highprismatic epithelial cells, although the lowprismatic were perhaps the majority. Practically every lumen had contents, although they did not fill them completely in the section. I shall make a more detailed report on these contents in the chapter dealing with aspiration of the amniotic fluid.

In the other cases no essential differences in structure could be found microscopically, except variations in the size of the lumina. (Table 5 gives an idea of these variations. See also Fig. 11, 12,13)

TABLE 5

Lumen Ratio in Stillborn Fullterm Human Fetuses

No.	I	III	Average
N 626/II/45	17 % ?	_	17 % ?
N 2659/II/45	15 %	15 %	15 %
N 1634/I/45	36 %	33 %	34,5 %
N 810/II/45	47 %	47 %	47 %
N 847/II/41	31 %	29 %	30 %
N 965/II/41	30 %	29/%	29,5 %
N 2246/II/45	20 %	19 %	19,5 %
N 2686/II/45	38 %	39 %	38,5 %

Th numbers signify: I right upper lobe III right lower lobe

In case N 2143/I/44 the fetus died evidently due to the prolapse of the umbilical cord. Macroscopically there was a scant quantity of air in both upper lobes. It is possible that it had entered the lungs in consequence of the insufflation recurred to. Microscopically the picture was in several sections similar to that described in the above cases. But there were some places where

the walls seemed straighter, more taut, the lumen was empty. In such places there was no twisting of the capillaries, they $\rm did$ $\rm Rot$ rise into the lumen in the same way as in airless places. There $\rm was$ not any considerable difference in the thickness of the walls, nor in the shape of the epithelial cells. The nuclei of the cells in the connective tissue were oblong in some places, but the difference $\rm was$ not distinct as compared to the airless area.

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In case K 643/46 there were no essential differences in the structure of the aerated areas compared to the above, although there were more air-containing areas and they were more widely spread. The walls were thick in part of the area. But in several places they were thinner than in the previous case. The epithelial cells were high-, iso- or lowprismatic also in the areas with extended lumina. It could not be found that the cells in these areas were lower than in the airless places. The capillaries were less full of blood and flush with the walls; they did not have a winding course. In some places the nuclei of the mesenchymal cells were elongated into a narrow ribbon-like shape, but this was not the case everywhere.

In case K 719/45 the lungs were nearly everywhere aerated, of a light colour, the pieces cut from them floated. Microscopically the alveoli were wide open, their walls thin, sometimes *hreadlike*. (Fig. 14) The tissue had but little blood, the capillaries were thin. Alveolar epithelial cells were isoprismatic, they could be clearly seen in the angles of the extended lumina, but sometimes some isolated isoprismatic cell could be found also on a straight part of the wall. In the walls the nuclei of the connective tissue cells were often long and narrow, unmistakably narrower than in the airless area. However, there were also fusiform nuclei that looked like mesenchymal cells. The histologic picture-of aerated areas in the other cases did not present any aspects essentially differing from what has been already described.

There are only 4 cases who, according to the delivery histories, were born asphyxiated and did not resuscitate. One of them had aerated areas both macroscopically and microscopically (case N 979/I/46). The microscopic picture was similar to what has been said above with regard to insignificantly aerated lungs. (e.g. case K 643/46). The microscopic picture presented by the others was such as

has been described above for airless lungs, the size of the lumina varying also from case to case.

Thus, these cases are not essentially different from those who had died in the course of the delivery.

The structure of the lungs with congenital atelelectasis on the basis of the cases described above is as follows:

The different lobes of the lungs present the same picture. Unmistakable lumina are to be found everywhere. In other words, the walls are not in close contact to each other. The walls are tort-110US, their thickness varies in different cases. It can often be noted that the relation between the thickness of the walls and engorgement of the capillaries, and on the other hand the extension of the lumina, is inversely proportional. The alveolar epithelial cells are high-, isoor lowprismatic, irrrespective of the size of the lumen. The mesenchymal lining cells are fusiform, their nuclei lie in the same direction as the course of the walls or slightly diverge from it. The thickness of the nuclei surpasses their length from 2 to 4 times. The nuclei in the capillary endothelial cells are twice to 4 times as long as thick, fusiform or crescent-shaped. The general aspect is intricate, with numerous compartments. The lumina have contents. -It is evident that these areas are congenitally atelectatic and clearly distinguishable from areas where respiration has occured.

The pulmonary structure of infants who had breathed during delivery has undergone the following changes: the tortuous course of the walls has disappeared. It appears as if the bulging capillaries and cells which caused the irregularity of the lining surface, were partly drawn into the wall. No essential changes can be noted in the shape of the alveolar epithelial cells, as there are high-, iso- and lowprismatic cells also in aerated lungs. The shape of the nuclei in the mesenchymal cells has sometimes undergone changes. They are narrower and longer than in lungs with congenital atelectasis. The capillary endothelial cells are perhaps somewhat narrower in aerated than in congenitally atelectatic lungs. Both these nuclei and those of mesenchymal cells show similar forms as in congenital atelectasis. The general aspect of the lungs has become less complicated, the walls being tense and their irregularities gone. Although it seems that alveolar epithelial cells occur less frequently than in congenital

atelectasis, this is a phenomenon that is probably due to the stretching of the walls. Thick (60—120 μ) sections show a great number of isoprismatic lining cells also in aerated lungs.

Alveolar contents are one of the important distinctive features of congenitally at lectatic lungs. Even if I do not in this connection make a more detailed study of the character of these contents, it is imperative to give a short exposition. Each of the preceding cases where no alveoli expanded by air were determined histologically, had alveolar contents. They do not always fill the whole lumen, but appear as precipitate, usually in its central part. Extended lumina are partly empty, but smaller lumina seem to be completely filled with the substance. This is not clearly visible in aerated lumina, and if there is some residue, it is found along the walls of the lumina. In addition to the forementoined substance, pieces can often be found which are skin epithelium cells or vernix caseosa. Their precense is not equally regular and their number greatly varies in different cases.

The microscopic picture of non-aerated lungs of fullterm feduses shows an essential difference among the individual cases only with regard to the lumen ratio (Table 5). On the other hand, each one is clearly distinguishable from aerated lungs. According to this study, the extension of the lumina does not have any significant influence on the finer structure of the lung in the human fetus, as long as the lung remains airless.

Conclusions can not be made on the basis of the cases reported above as to the fetal state of the lungs. As illustrated by table 11, they all show either signs of intra-uterine asphyxia or there was a complication during delivery which can be regarded to have caused premature respiratory movements and in this way, dilatation of the lungs. It is not at all evident that those lungs where the lumina were more extended should have been subjected to the influence of a factor producing stronger respiratory movements. Such knowledge as we have at our disposal does not allow of making any conclusions with certainty in regard to this question. It is further impossible, on the basis of these cases, to determine the size of the alveolar lumen at the moment of birth, before the inhalation of air in such cases where there were no factors disturbing the umbilical circulation. In one respect all these cases are similar: the

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injurious factors directed against the baby during delivery were so strong that they caused death.

Live-born Infants. Aeration of the Lungs.

It is not possible to determine on the basis of my material how quickly the lungs become aerated in infants who are going to live and have a good respiration. Such infants as die in the course of the first few days after birth usually suffer from diseases or faulty development that have a restraining influence on the respiration and the rapidity of aeration of the lungs. One can therefore say that the results obtained from post mortem material represent in the first instance the slowest aeration.

My material is such that it is not possible to exclude from it cases where factors delaying the aeration are absent. However, I omit, to begin with, all those where factors greatly delaying the expansion of the lungs were to be found in the lungs themselves. I have therefore excluded all cases where formations of membranes could be ascertained. (See chapter concerning aspiration of the amniotic fluid). I am also omitting cases that showed an unmistakable disorder of the intra-thoracic development (Diaphragmatic hernia — cases N 967/II/45, N 534/II/45). The cases indisputably remaining also have a great number of factors influencing the respiration, but, as already said, it is impossible to obtain material that should not have any factors exercising influence on the respiration.

When determining the rapidity of the lungs' aeration with the aid of my material, I have been able to use as a basis of estimation nearly solely the circumstance, how soon the congenital atelectasis disappears (see animal experiments p. 40). When congenital atelectasis is used as a basis of determination it is imperative to draw a division between it and secondary atelectasis. It was possible to determine in the animal experiments the histologic difference between these two forms of atelectasis. In the post mortem material, there is a difficulty of finding a starting point, as it is hard to determine some area which has with certainty become atelectatic in a secondary manner.

As already-mentioned in the survey of literature (p. 25), vernix membranes have been found only in aerated lungs, and it is consi-

dered that respiration is a necessary factor for their appearance. (My own researches point in the same direction). It can therefore be considered most probable that areas where these membranes are met with, have breathed. As these membranes are sometimes demonstrable also in atelectatic regions, the latter can be regarded as a type of a secondarily atelectatic area. The possibility cannot be denied that these can have partly collapsed first after death. In these cases also they represent aerated areas which have afterwards become airless.

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Case N 494/II/45 had rather extensive atelectatic areas, where membranes could be found. (See Fig. 15) This baby had survived for 27 hours. Its condition after birth was good, according to the history of delivery. Microscopic examination of lungs revealed a great quantity of membranes in all sections. All the lobes showed atelectatic areas. The right lower lobe had the largest amount. When examining the atelectatic areas one could clearly dintinguish small lumina covered with membranes. The walls were torthous, The shape of the lumina was irregular, both shape and size varying greatly. The walls were thick. The capillaries were rather full of blood, bulging somewhat into the lumen. The nuclei of their endothelial cells were oblong. It was difficult in some places to find alveolar epithelial cells. The form of the cells was low- or isoprismatic, but highprismatic cells were also found. There were 1-3 cells in one place - usually they were isolated. The plasma stained but slightly. The nucleus was round or oblong, sometimes angular or lengthened. Part of the nuclei was dark, without structure (pyknotic). The nuclei of the connective tissue cells were oblong, rather short, sometimes looking twisted. As a whole the tissue had an irregular appearance and seemed sin disorders, and it was sometimes difficult to distinguish among different kinds of cells.

These characteristics of secondary stelectasis conform rather closely to the picture which was obtained by means of animal experiments of lungs with secondary atelectasis, and correspond to the changes observed in aerated lungs. In order to draw the division between congenital and secondary atelectasis in each case one must try to establish, what are those essential and typical characteristics that divide these two forms of atelectasis from each other. The lumen size is no essential difference, as according to what has been

explained above, this size can greatly vary in lungs with congenital atelectasis. It seems however that the average variation is less in

TABLE 6

Characteristics of Congenital and Secondary Atelectasis in Lungs of Fullterm Infants

	Congenital atelectasis	Secondary atelectasis
Size of lumen	Small variations in same case	Wide variations in different places
Thickness of walls	Small variations. Generally thin	Wide variations. Often ap- pear thick
Course and shape of wal!	Tortuous course	Straighter course
Capillaries	Engorgement varies. Capillaries clearly distinguishable from walls, bulging out into lumina	Engorgement varies. Capil- laries mainly on level of walls
Endothelial cells	Nuclei crescent-shaped or fusiform	Nuclei crescent-shaped
Alveoral epithelial cells	Clearly dinstinguishable from walls	Flush with walls
Form	Hight-, iso-, lowprismatic	High-, iso-, lowprismatic
Nucleus	Round or elliptic, in centre or basally	Round, elliptic, angular generally in centre
Arrangement	1—3 in same place, of dif- ferent shapes. Arrange- ment often irregular	1—3 in same place, of dif- ferent shapes. Arrange- ment irregular
Mesen chymal cell nuclei	Fusiform, length exceeds thickness 2-4 times	Ditto
General aspect of lung	Regular, different places present same aspect. »Nice» structure	Irregular and varying ap- pearance. «Coarser» struc- ture

lungs with congenital than with secondary atelectasis. It also appears that the thickness of the walls varies less in congenital than in secondary atelectasis. Owing to these features, the structure of a lung with congenital atelectasis is more regular than in lungs affected with secondary atelectasis. Table 6 illustrates the characteristic features in different parts of a lung with congenital and secondary atelectasis. It is difficult to determine, to what an extent the characteristic features of secondary atelectasis described here can also be present in congenital atelectasis of a longer persistence. On the basis of animal experiments, it appears as if the areas must first become aerated before they are affected with secondary atelectasis.

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When dealing here below with the rapidity of the inflation of the lungs, whose basis is the disappearance of congenital atelectasis, I did not consider myself justified in regarding as congenitally atelectatic other areas than such as have shown the characteristic features of it described above. It must be admitted that the basis of estimation is not quite free from possible errors. It is however practicable to check the results to a certain extent with the help of such cases that are free from atelectasis. Although the clinical knowledge is often incomplete, it still helps in the estimation of the cases. This being so, there are some possibilities to estimate the rapidity of the aeration of the lungs also on the basis of this material, duly considering the limitations described above.

The youngest case who showed strongly inflated lungs, died in the course of the delivery (Case K 719/45). The greatest part of the lungs was aerated. They were throughout of a mosaical light colour. Microscopical it was possible to ascertain that the basal parts of both lower lobes had unmistakably airless areas. The borders of these areas were very distinct (See Fig. 14). The airless areas were very few. The infant having died in the course of the delivery, this case proves that very extensive areas can become fully aerated as a result of only a few respiratory movements. It must be noted that the extended lumina were generally open *to the utmost* and the walls thin, threadlike. Although smaller lumina could also be found in several sections, they had unmistakably tense walls. Thus only the basal parts remained airless. Large areas of the dorsal parts were also aerated.

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TABLE 7

Aeration of the Lungs in Fullterm Infants free from Membranes

Atelectatic Areas in Different Lobes

	I		I	I	11	I	I	V	V	
No and age.	Ca	Sa	Са	Sa	Ca	Sa	Ca	Sa	Ca	Sa
N 458/I/45	+		+	_	+	_	±		+	_
18 min. K 1823/45	+	_	+	_	±		+		+	_
3 ½ hours					-					
K 2399/45 B	±		土	-	++	-	+?	+?		++
N 2780/I/45	± .	-	土	-	++	-	土	-	±	-
1 ½ days N 1255/II/45	±		-	土	+	-	土	-	+	-
2 days L 100/46	土			-	+	-	土	-	++	_
2 days N 829/I/41	_	+	_	_	± ?	_	± ?	+	±	±
2 days										
N 845/H/46	±	+		+		++	土	+	-?	+
2 days K 862/45	_	±		±	-	土	_	_	± ?	± 1
2 days P 358/45	++	-	_	_	±	±		± ?	±	+
3 days										
L 261/47	-	-		-	-	土	-	-	-	-
7 days L 272/47		_	_	_	_	±	_	_		+
7 days										
P 363/45	-	-	-	-	_	土			-	土
11 days L KP/45	_			-		+		_	_	-
11 days					-	1				
L 122/45 1 month	-	±	-	-	-		-	-	-	土

Signs: — no atelectatic areas, \pm small atelectatic areas, + middlesized atelectatic areas which do not comprise half of the area of specimen, ++ atelectatic areas being half or more of the area of specimen.

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Ca= congenital atelectasis, Sa= secondary atelectasis, I= right upper lobe, II= right middle lobe, $\,III=$ right lower lobe, $\,IV=$ left upper lobe, $\,V=$ left lower lobe

Table 7 illustrates the presence of congenital and secondary atelectasis in lungs free from membranes where respiration has occurred applying the above methods of determination. I have also paid attention to the contents. The precipitate appearing in congenitally atelectic lungs has no such definite character that it could not be regarded as due also to other reasons. A substance of a similar appearance is sometimes met whit also in lungs of older infants. Its absence gives however an indication to the effect that the area had become aircontaining, as this substance could be found in the lungs of all stillborn infants. No absolutely certain division between congenital and secondary atelectasis could be drawn in the areas of each one of the cases illustrated by the table. In the majority of cases however I find that the difference was sufficiently evident.

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It can generally be seen in a lung that has breathed only for a short time and become only partly aerated, how only a part of the alveolar tree is expanded, and its peripheries retain flabby walls and small lumina. (Fig. 16, 17) This is regularly found in the lungs of infants who died in the course of the first three days of life. The same findings can be made in the lungs of those who died during delivery or were asphyxiated and did not resuscitate. The case K 719/45 (see above) is an exception, where the lumina were extended and the partitions thin in a throughout aerated area (See Fig. 14.) When the alveolar tree is only partly air-containing, its peripheral parts generally have morphologically the appearance of congenital atelectasis. This can therefore be considered to some extent as a normal phenomenon in the aeration of the lungs in cases where it takes place slowly. It is not possible to maintain on the basis of my material that this should always be the case - also if the aeration is rapid. To the contrary, case K 719/45 speaks against such a supposition.

When examining as a whole the clinical picture and the post mortem findings of the cases presented in table 7, we get an idea as to what an extent the aeration of the lungs can be regarded as possibly differing from corresponding »normal cases». (See table 12). It is to be noted then that nearly all were in a serious pathologic state, which can be considered as having exercised an influence on the character of the respiration. The six youngest infants had serious

asphyxia and several had had an impeded respiration the whole time. The seventh had a difficult respiration and the post mortem revealed a congenital heart disease, which must be considered to have made the continuation of life impossible. Congenitally atelectatic areas were found in all these cases. The youngest, of whom the delivery history does not say anything with regard to respiratory disturbances, were two days old (Cases N 829/I/41 and N 845/II/46). One of them revealed a cerebral hemorrhage, the other rupture of the liver and hemorrhage into the abdominal cavity. Both cases show small areas of congenital atelectasis. Case N 845/11/46 can be taken to have breathed well at first, and to have therefore approached the »normal». These cases have larger areas affected with secondary than with congenital atelectasis. Case K 862/45 is normal in so far, as nothing pathological was observed during the first day of life, and the baby died unexpectedly and suddenly. The lungs did not show at all any unmistakable areas with congenital atelectasis. The left lower lobe had small atelectatic areas of which it was impossible to say whether they were congenital or secondary. In an infant aged three days who was sleepy and slow to react (case P 358/45) and in whom the post mortem revealed a cerebral hemorrhage, areas were found in the lungs that could be regarded with certainty as congenital atelectatic. Only in the lungs of an infant a week old was it possible to establish a total absence of congenital atelectasis (L 261/47). This baby died suddenly.

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As illustrated by the table, the lungs are aerated everywhere only as late as in infants about two days old — up to that time extensive atelectatic areas are to be found at least in one lobe (marked on the table + or ++), and not only a few areas or a penetration of air into some part of the alveolar tree only (marked on the table \pm).

Although the microscopic examination revealed that the lung was air-containing everywhere, and there were even no sections of the alveolar tree unmistakably airless, the walls seemed to be of a different thickness. Case K 719/45 had thin threadlike walls, but in case K 862/45, which was aerated throughout, the walls were quite clearly thicker. In a baby who had lived 7 days the walls were again unmistakably thinner — and this was also the case in

an older infant. It can therefore be said that the aeration of all sections and consequently the absence of atelectasis does not prove that the lung is fully expanded, but also such cases who have these characteristics show an aeration of different degrees. This circumstance makes a comparison of the aeration in different cases more complicated than can be supposed solely on the basis of a macroscopic examination. — It must be admitted of course that post mortal changes can partly cause differences, therefore one must be careful when making conclusions on the basis of these findings.

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Conclusions. — The lungs can become almost completely aerated alreadey after a few inspirations.

The lungs in my post mortem material were unmistakably acrated everywhere in infants 7 days old. However, already such infants who had died aged 2—3 days, can have lungs nearly free from congenitally atelectatic areas. In such cases there have generally been factors which weakened the condition of the baby. Atelectatic areas persisted for the longest period of time in the lower lobes. Secondary atelectasis can already be found in infants one day old. Cases who do not have atelectatic areas, are exceptions in the post mortem material.

The aeration of the lungs where membranes could be found will be taken up in connection with the aspiration of amniotic fluid.

Premature Infants

Stillborn and Asphyxiated who Did not Resuscitate. Congenital Atelectasis.

There are only five stillborn infants in my material weighing < 2500 gm, the weight varying from 670 to 2000 gm. One of them died during pregnancy (Case K 591/45). The weight at birth was 1930 gm. The fetus was somewhat macerated. The inner organs were soft. The lungs were macroscopically airless. Microscopically all sections presented a similar picture. Lumina were demonstrable in the alveoli. Their epithelial cells had for the most come off. The shape of the cells adhering to the walls was high- or isoprismatic. The erythrocytes were clearly visible in the

capillaries and judging by them there was a great number of capillaries.

The smallest of those who had died during delivery were the twins K 425/45 A and B. - The weight of the B-fetus at birth was 670 gm. Macroscopically the lungs were airless -- the surface did not show anywhere aerated areas, but had the same appearance throughout, of a greyish-red colour. Microscopically it was possible to determine that the lumina of the anterior part of the right central lobe were unmistakably more extended than elsewhere. There were no significant variations otherwise, either when measuring by the eye or counting the lumen ratio (see table 8). In the areas with small lumina (8-10%) the cells lining them were high or isoprismatic. (Fig. 18. See also Fig. 23) They were lining the main part of the lumen but here and there loops of capillaries could be seen among them in direct contact with the lumen. Protoplasma in the cells stained either feebly or not at all. The nuclei were oblong or round, lying in the centre of the cell or somewhat eccentrically, when they where often farther away from the base than from the surface. The diameter of the nuclei was about half of the diameter of the cells. The alterations of the forms of the cells were usually insignificant, - yet there were sometimes cells strongly differing in shape from the others in the lining of the same lumen (highprismatic, isoprismatic). The arrangement of the cells was often regular, but sometimes not — there were places where the lumen was insignificant and it could then be noted that they had formed epithelial layers. The abundance of capillaries varied in different places and it was often possible to find capillaries only in the basal parts of the epithelial layer; their coils did not in that case penetrate among the epithelial cells. The extension of the capillary coils which reached the lumen varied from areas of the width of one epithelial cell to areas corresponding to the width of 3-4 such cells. The nuclei of the capillary endothelial cells were clearly visible. The extreme periphery (pneumonomeres) were most deficient in capillaries, and the greatest capillary coils lay in the somewhat more central parts. The lumina were generally empty. The whole had an appearance of regularity and the lumina were clearly distinguishable by reason of their light epithelium. The tissue between the cavities was loose,

its cells had oblong or fusiform nuclei. It was not clearly distinguishable by staining from the epithelium, the only difference being that the protoplasma in the cells took on a somewhat stronger staining. Nothing was seen there that resembled a staining proper to connective tissue. Only around the blood vessels there were collagenic and elastic fibres. The sections had some places where cells with the exact appearance of epithelial cells formed an islet devoid of lumina within the tissue, that was clearly bounded by the surrounding loose tissue. There were also similar islets formed by a few cells and also places where the lumen was quite insignificant. I have regarded these forms as being caused by a dissection of different places.

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The weight at birth of twin A was 850 gm. In the anterior part of the lungs it was possible to distinguish very few light-coloured aearated areas, differing from the rest of the tissue. Microscopically the structure of the lungs was not different to that of the B-fetus.

Case N 352/II/45 (weight at birth 1040 gm) did not reveal macroscopically any areas differing from the rest of the structure. Microscopically there was a small area in the right lower lobe with extended lumina. (Fig. 19 — see also Fig. 28.) Elsewhere they were small but distinct. The structure differed clearly from the preceding. The cells lining the lumen were of the same form as above, but they did not line the lumen nearly as uninterruptedly, there being usually 2—5 cells close to each other and coils of capillaries in the spaces between. The capillaries were unmistakably more abundant than in the cases K 425/45 A and B. The walls were thinner — they appeared now as partitions and the aspect was not at all similar to the above where the epithelial part was seen as some kind of an islet in the loose mesenchymal tissue. The tissue in the walls was not different to what has already been described.

Case N 1521/II/45 (weight at birth 2000 gm.) showed macroscopically an area in the front part of the right central lobe that was clearly different from the rest, as it was of a light colour and air-containing. A microscopic examination revealed here extended lumina, but the size of the lumina varied greatly. (Fig. 20) There were also extended lumina in the left upper lobe, but a very small number of areas without any lumina could also be noted. The tissue structure greatly resembled the lungs of fullterm fetuses —

yet there were unmistakably more alveolar epithelial cells and less capillaries than in the fullterm. The cells had an iso- or highprismatic form.

TABLE 8

Prematures who Died During the Labour

Lumen ratio

Number	Birth		Lumen	rati	0 (%		
	weight	I	II	Ш	IV	V	Remarks
K 425/45 A	850 gm		12	13	10	12	Aeration
K 125/45 B	670 gm		19-13	9	10	8	
N 352/II/45	1040 gm	7	5	6			Area in III where lu men ratio 34 %
N 1521/II/45	2000 gm	25	80	15	3	_	In II part as in III and part is extended, where lumen ratio counted

 $\begin{array}{l} \mbox{Signs: I = right upper lobe, II = right middle lobe, III = right lower lobe,} \\ \mbox{IV = left upper lobe, V = left lower lobe.} \end{array}$

Table 8 illustrates the lumen ratio in the lungs of prematures who died during delivery. Even if it is not possible to make any conclusions on this basis as to the extension of the lumina in the fetal state, any better than with regard to the fullterm fetus, it can yet be maintained that lumina are to be found everywhere in the lungs of stillborn premature infants. As already mentioned in the survey of literature, there are according to Bender's researches unmistakable lumina in the pneumonomeres during the whole evolutionprocess of the lungs. The method of calculation described above yields different results regarding the relative size of the lumen in the fullterm and the premature infant -- especially for the smaller premature - owing to the circumstance that when counting as described, the extensive tissue area between the pneumonomeres proportionally reduces the lumen ratio. Taking this into consideration, it can still be maintained that the lumina look smaller in the premature than in the fullterm baby. The microscopic structure of congenitally at electatic lungs of the premature is different in different cases, depending on the stage of development of the fetus. In the

fetus who had the lightest weight in my material the cells lining the lumen were mainly high prismatic. With the increase of the weight at birth it appears that the relative proportion of the cells decreases and at the same time the number of capillaries reaching the lumen grows. A regular structure of the tissue is characteristic of congenital atelectasis.

Live-Born Premature Infants. Aeration of the Lungs.

The preceding reports show that the difference in structure of the lungs of premature infants depending on their weight at birth is so significant that it appears advi able to make a special study of the aeration in different weight groups. Accordingly, I have divided my material into two groups *Immaturus* (weight at birth < 1250 gm) and *Praematurus* (weight at birth 1250—2499 gm).

Immature Injants. — There are twelve cases in all. Only four of them are such where no membranes were demonstrable. They all died in the course of the first 24 hours. Table 9 presents their weight at birth, age and aeration of the lungs. The difference is most pronounced between the two who had lived longest (N 210/H/ 45, L 26/46) and is evidently greater than what could be expected as due solely to the difference in the term of life. In both cases a subdural hermorrhage was found, which was regarded as the cause of death. The sections of lungs show an unmistakably different structure — especially in the abundance of capillaries. The baby with the greater weight at birth showed a larger number of capillaries attaining the lumen than other one with the lesser weight. No difference was evident regarding the form of the cells, because case N 210/II/45 had post mortal changes hampering the estimation. The pulmonary structure of the three with the lightest weight at birth showed but little difference, both with regard to the structure itself and to the expansion of the lungs. The aeration was insignificant everywhere and limited to the central part of the alveolar tree that was not fully developd. The structure of the parts with small lumina was the same as described above in case N 352/II/45. There are variations in the number of capillaries, but not sufficient to be demonstrable when measured by the eye.

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TABLE 9

Aeration of the Lungs in Immature Infants free from Membranes

Number	Birt weight	Aye	Aeration				
N 446/I/45	1020 gm	1 hour	Peripheral parts of sarbor alveola lariss not expanded, their lumin small. sBronchiolis and salveola ductss have tense arched wall in places. In right middle lobe salveolars lumen also somewhat expanded.				
N 852/I/45	980 gm	2 h. 15 min.	Rather similar to the above.				
L 26/46	970 gm	19 hours	Clearly extended lumina — in main part of right middle lobe up to periphery, similary in some places of upper lobe. Otherwise as above.				
N 210/II/45	1240 gm	23 hours	In all lobes expanded areas reaching periphery — estimated at half the area of section, in right middle lobe more than half.				

The material comprises a case with a weight at birth of 970 gm, who had lived for 5 days (P 203/45), and had a scant number of membranes. *) A structure unmistakebly different to what has been described above in connection with congenitally at electatic lungs, was found in the left lower lobe with a half-collapsed lumen lined by membranes. (Fig. 21) The cells had an irregular form, vaguely fusiform, and appeared to be flush with the wall. The cells did not appear in regular formations, but one or two together, and the variations in shape among them were considerable. The cell nucleus was oblong or angular (often dark, pyknotic). The total number of cells seemed to be much less than in a stillborn immature infant of the same weight. On the other hand, the number of capillaries

^{*)} The specimen taken from the right upper lobe of this case showed inflammatory changes in a restricted area, mainly however in the *bronchioli*.

appeared greater. The difference from congenital atelectasis was very much pronounced. There was every indication that these areas were affected with secondary atelectasis. Their tissue structure can be considered as characteristic of secondary atelectasis. It is to be noted especially that also the shape of the cells in this case is clearly different to that of the lung with congenital atelectasis. (Compare with results of observations on lungs of the fullterm infants). This variation in the cell shapes conforms to Farber's observations.

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With a view to studying these differences of structure, I have deemed it advisable to examine other immatures in whom membranes were found. In addition to those described above, there were seven such cases in all. In case N 935/I/45 (weight at birth 1090 gm and age 6 1/2 h.) two kinds of lumen, regular and irregular, were clearly distinguishable. In the irregular lumina the cell form was also irregular, isoprismatic or lower. The cells had the appearance of being plastered along the walls and took on sometimes a fusiform shape. The contours of the lumina were irregular here — the walls tortuous. There were often membranes in the irregular lumina, but they were absent in regular ones. There were also some irregular without membranes. The supposition seems justified that those with an irregular shape are areas affected with secondary atelectasis In other subjects placed into the immature group because of their weight an irregularity of the shape of the lumen was found in such areas which were probably secondarily atelectatic. Alterations in the form of the cells were much rarer and difficult to determine, It is noteworthy that the majority of the cases died during the first 24 hours, which tends to show perhaps that such changes need a longer time. When estimating the character of atelectatic areas in the lungs of immatures who survived for a short time, it can therefore be said that it is clearly more advisable also in these cases to study the irregularity of the lumen rather than of the cell forms in order to differentiate between congenital and secondary atelectasis, although the shape of the cells can also be of use in the estimation.

As illustrated by table 9, the expansion of the lungs of the immatures often had the same character as in the fullterm lung—i.e. only part of the alveolar tree had become aerated, while the peripheries retained their congenitally at electatic structure. Yet in immatures less than 1000 gm weight and under a day old, lumina

could already be found that were extended up to the extreme periphery (case L/26/46). Case K 720/45 (weight at birth 920 gm, age 1 $\frac{1}{2}$ h) proves that some part of the immature lung can become fully aerated within a short time. This subject had but a small number of membranes. In a specimen taken from the right central lobe all the lumina were expanded to the utmost. (Fig. 22) This expanded area showed in some places isoprismatic cells up to 8 one after another, and the cell form was isoprismatic, the cells being similar to each other as to shape and clearly distinguishable from the other parts of the walls. In the whole material there was only one immature in whose lungs no congenitally at lectatic areas could be found (P 203/45). — This case died 5 days old.

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In case P 203/45 it seems that the number of capillaries extending up to the lumina was considerably greater than in other immature babies of the same weight who had died in the course of the first 24 hours. In the other cases it was not possible to find more capillaries extending into the lumen, in the aerated than in the congenitally at electatic areas, and it does not therefore seem justified to draw any definite conclusions on the basis of the case in question. The ability to distinguish capillaries in sections of this kind greatly depends on their engorgement, which hinders the comparison between different cases and renders it uncertain.

With regard to areation of the lungs of immature infants, the following can be maintained on the basis of this material: The lungs did not become fully aerated everywhere in the course of the first 24 hours. Some part of the lung can then be air-containing in such a way, that the lumina are open up to the extreme periphery—already in babies under two hours old. Lungs of infants who died five days old can be free from congenitally atelectatic areas.

Premature Injants. — My material comprised 11 premature infants free from membranes and under two weeks of age (not counting the immatures). One of them had diaphragmatic hernia. (K 970/41). The weights at birth of these infants varied between 1270 and 2430 gm and their age was from 13 minutes to 9 days.

The differentiation between congenital and secondary atelectasis in the premature is possible along the same lines as described above

where fullterm and immature babies were concerned. Although the lungs are different as to structure from the lungs of fullterm infants, the premature are nearer the fullterm than the immeture with regard to structure of the epithelial cells and the umber of capillaries. This is naturally most evident in those whose weight at birth approaches 2500 gm, ut even close to the nether limit the structure greatly resembles that of fullterm babies. The difference lies in the circumstance that, when measured by the eye, the premature have less capillaries and more epithelial cells than the fullterm. Yet the borderline is by no means pronounced, and therefore it is possible to meet with cases in this group approaching the nether limit, where the pulmonary structure greatly resembles that of the immature (case N 788/I/45 — weight at birth 1360 gm.). (Fig. 23) Such aspects can also be seen in infants with a considerably greater weight at birth (K 2621/45 - weight at birth 2080 gm.). (Fig. 24) There is however a difference in the forms of the cells lining the walls, especially when compared to those weighing under 1000 gm, as the majority of the cells in the premature are unmistakably lower -- they are isoprismatic, whereas the cells of the immature are mainly high prismatic.

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The quantity of capillaries reaching up to the surface of the lumina is some kind of a criterion of the development of the lungs. It is however evident that when examining the number of capillaries in an ordinary section, only such capillaries where there is blood, are seen and taken into consideration. Capillaries empty of blood, on the other hand, are so difficult to find, that it is impossible to make any comparisons of the quantity of capillaries on the basis of such studies. It appears evident that there are individual variations in the quantity of capillaries, nor does their quantity solely conform to the variations of the weight at birth.

In order to draw the division between congenital and secondary atelectasis. I have made use, in the first place, of the differences in the shape of the lumen and in the position of the epithelial cells on the walls. I have also paid attention to the form of the cells, and it seems as if these also underwent sometimes variations similar to those described above in case P 203/45. I feel this has been the case with subjects whose weight at birth was under 1250 gm or thereabout. In case P 76/45 (weight at birth 1300 gm — age 9

days) the cell form was low, irregular, but there were also to be found isoprismatic cells of a regular shape in lumina of an irregular form and where the position of the cells on the walls was the same as in lumina with secondary atelectasis.

Although the pulmonary structure is different in different cases of premature infants, and the differentiation between congenital and secondary atelectasis sometimes difficult, I have endeavoured to illustrate by table 10 the aeration in the lungs of my cases free from membranes. According to this, the lungs of these cases did not expand fully in the course of the first three days, congenitally atelectatic areas being noticeable in one or several lobes. As already mentioned, there are cases where it is difficult to determine whether some area is affected with congenital or with secondary atelectasis. This is e.g. the case with subject K 1019/45. Here lumina could be seen that had a regular form, and the form and arrangement of the cells where exactly as in congenitally atelectatic lumina. But there were others of a regular shape, with 3 to 4 isoprismatic cells close to each other rising from the walls in regular formations, and a lumen with every appearance of secondary atelectasis could be seen in the close vicinity. In such cases I did not feel I had any certainty as to whether the said area was to be considered congenitally or secondarily atelectatic. The examination of extended lumina after breathing has revealed that even when the lumen unmistakably expands, some cells can retain their shape and the position on the walls characteristic of lungs with congenital atelectasis. - In cases where such questionable cells were in evidence, it was however often possible to find areas which were undoubtedly to be regarded as congenitally atelectatic, therefore this circumstance is of no particular significance where a general estimation is concerned.

When studying the post mortem findings and clinical observations on the prematures, such pathologic states can be found very often, which may be thought to have influenced the respiration. A considerable part had intracranial hemorrhages and mention was often made in the reports of a respiration impeded in some way. (See table 14).

It is therefore evident that post mortem material reveals a most slow aeration, and it is quite possible that it takes place much more

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TABLE 10
Aeration of Lungs in Premature Infants free from Membranes

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No birth- weight and		I	1	II	1	II	1	IV	1	v	Parr
age	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Remarks
N 788/I/45 1360 gm	++	-	++	-	++	-	++	-	++	-	
13 min. K 2621/45 2080 gm	++	_	++	_	++	-	++	-	++	_	
30 min. N 717/I/45	±	_	_	±	±	±	±	±	±	±	
2150 gm 9 ½ hours											
K 1919/45 A 2430 gm	±	±	± ?	士?	+	_	± ?	±?	+	-	
22 hours N 1043/I/41 1750 gm 18 ½ hours	±	_	_	_	±	±	±	_	-	+	
L 129/47 2000 gm 2 days											Lumina full
P 370/45 1270 gm	-	±	-	±	-	+	±	+	±	+	extendet, but struc- ture blurred
3 days P 172/45	_ 1					±				±	by blood
1300 gm 4 days											
N 463/II/45 2180 gm	±	±	-	-	±	±	±	± -	-	± ?	
days L 108/47	- -	++	_ -	++	-	++	_	+ -	-	+	
620 gm days 76/45	_	± -		_	_?	±	±	± -		±	
1300 gm days											

Signs: — no atelectatic areas, \pm small atelectatic areas, + middlesized atelectatic areas which do not comprise half of the area of specimen, ++ atelectatic areas being half or more of the area of specimen.

 $\begin{array}{l} \mathbf{I} = \mathbf{congenital} \ a \mathbf{telectasis}, \ \mathbf{Sa} = \mathbf{secondary} \ a \mathbf{telectasis}, \ \mathbf{I} = \mathbf{right} \ \mathbf{upper} \ \mathbf{lobe}, \ \mathbf{II} = \mathbf{right} \mathbf{obe}, \ \mathbf{III} = \mathbf{rightlowerlobe}, \ \mathbf{IV} = \mathbf{leftlower} \ \mathbf{lobe} \end{array}$

rapidly in healthy undamaged prematures with unimpeded respiration, than in those who have been the object of this study.

Conclusions

The lumen of unaerated areas in the lungs of stillborn premature infants is small, but its presence can be established in any case. The lumina are smaller than in the fullterm babies, but the material does not justify conclusions as to the growth of the lumen according to an increase in weight. Estimation is rendered more difficult by the circumstance, that the lumina may be extended in consecquence of premature respiratory movements due to the effects of labour.

In aerated lungs no distinct difference can be ascertained in the mode of expansion. Both in fullterm and premature babies the lumen may often expand in such a way, that only a part of the alveolar tree in the process of development expands, whereas a part remains congenitally atelectatic. Yet all the lumina can be extended *to the utmost* in some part of the lungs of immatures under 1000 gm weight at birth. Such an extension can also be seen in small areas in babies who died during the delivery. In consequence of differences in the pulmonary structure it is not possible, where the prematures — and also the immatures are concerned, to establish a histologic difference common for all between congenital and secondary atelectasis, as this is possible with regard to fullterm babies. The difference lies in the alterations in the shape of the lumina and of the cells in their walls.

My post mortem material speaks on behalf of a gradual aeration in the lungs of prematures, so that lungs that are or have been fully aerated can only be found in babies who had survived for 4 to 5 days. It is evident that on the basis of this material no conclusions can be drawn as to how quickly the aeration takes place in healthy undamaged prematures. However, the material speaks for the supposition that the aeration is gradual also in these latter, as congenitally atelectatic areas were revealed by autopsy in infants three days old also in such cases, where nothing special could be found in the state of the baby after its birth.

The aeration is perhaps somewhat slower in premature than in full term infants, but according to this material, the *utmost* rapidity is not so very different for both these groups.

2. On Amniotic Fluid Substances in the Lungs

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The cases are divided into two groups, with or without membranes in the lungs. I have however deemed it advisable to deal partly in both groups with stillborn and asphyxiated infants who did not resuscitate.

It is easier to determine and in different cases to compare the amount of aspirated substances in the group free from membranes than in the other. Even in such cases the comparison is rendered more difficult by the circumstance that the amounts cannot be compared to each other numerically. The counting of the squameous epithelial cells of the amniotic fluid in the lumina would hardly be of any use, because it is to be supposed that their number in the amniotic fluid varies in individual cases. This holds evidently good also with regard to drops of fat. The precipitate constantly found in the lungs of the stillborn probably has its origin in the liquor amnii - at least partly. It is very difficult to determine the amount of this material. It must be taken into consideration that with the preparation of the section, some substances may have become detached from the lumen, and their amount can be different in different cases. I have not endeavoured to make any exact estimation, but have contented myself with very summary estimations of the amounts of different substances in the lumina. I have marked the amounts of these substances on the tables as \pm (small), + (medium) and ++ (abundant). I have endeavoured to apply the same scale in different cases, as much as this was feasible when measuring by the eye. I have not paid any attention to the quantities of lanugo hairs and meconium in the lungs, as these make the estimation of the extent of the aspiration even more difficult than by means of the above principles.

Cases free from Membranes

I shall deal at first with fullterm and premature infants as two different groups.

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Epithelial cells and squamae from the amniotic fluid were to be found without exception in the lungs of infants who died during pregnancy or at birth, and of the asphyxiated who did not resuscitate. Table 11 illustrates the quantities of the substances found estimated according to the abovementioned method. If the amount of particles (i.e. epithelial cells and squamae of the amniotic fluid) in the lumina is taken as a basis, strong aspiration had occurred in 5 cases who died during delivery. Compression of the cord was found in three of them. In two others the amniotic fluid was discoloured, and in one of them a deterioration of the fetal cardiac sounds could be established during labour. The strong aspiration in these cases can therefore be considered as due to intrauterine asphyxia. On the other hand, there were five who died during pregnancy or at birth, where compression of the cord was present, but a medium (three cases) or small (two cases) quantity of patches was found. In three other cases who died during delivery there was a medium quantity of patches. In two of them observations were made which may be taken as an explanation of the aspiration that had occurred (cases N 965/II/41 and K 3189/45). One case had an insignificant amount of substances (N 847/II/41) and nothing special was said about the delivery, but that it had lasted for a long time. This case can be regarded as representing the »physiological» aspiration. It must be admitted, that this case diverges so much from an ordinary delivery, that the aspirated amount need not be such where labour has proceded without disturbances.

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In addition to the forementioned particles, fat drops were a constant finding. Their quantity was generally about similar to that of the liquor amnii epithelial squamae and cells. There were some exceptions. As the fat substance in the amniotic fluid can vary in individual cases, it is easy to understand that the amount of aspirated fat drops also can vary due to this reason. When staining frozen sections, e.g. transferring them from one staining solution to another, one runs a greater danger of the substances dripping away than when staining paraffin sections, in which case the specimen is fixed on glass. I therefore feel that the idea gained from paraffin sections is nearer the truth than that given by staining fat. I have

TABLE 11
Aspiration of Amniotic Fluid in Fullterm Stillborn and Asphyxiated Infants who Did not Resucitate

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Number	Aspiration quantity	Intra-uterine asphyxia	Complications of labour Post mortem findings
N 626/II/45	Particles + Other subst. ++ Fat +	Discoloration of am- niotic fluid	Umbilical cord squeezed in hand of fetus. Ecchymose-
N 2659/II/45	Particles + Other subst. + +	Cardiac sounds cea- sed, no other obser- vations	Ecchymoses
N 1634/I/45	Particles ++ Other subst.+ Fat ++	Strong discoloration of amniotic fluid	Ecchymoses
N 810/II/45	Particles ++ Other subst. ± Fat ++	niotic fluid. Cardiac	Ecchymoses
N 847/II/41	Particles \pm Other subst. $++$ Fat \pm	Amniotic fluid ordinary	Prolonged labour Leptomeningeal edema
N 965/II/41	Particles + Other subst. + Fat +	Discoloration of am- niotic fluid	Pelvic presentation Congenital hydro- cephalus
N2246/II/45	Particles + Other subst. ++ Fat +	-	Strangulation by the cord. Congenital hydronephrosis
N 2686/II/45	Particles + Other subst. + + Fat +	Amniotic fluid ordi- nary. Cardiac sounds weakening then ceas- ing	Prolapse of the cord
K 719/45	Particles ++ Other subst.+ Fat ++	Amniotic fluid some- what discoloured	Strangulation by the cord. Subdural hemorrhage
N 2143/I/44	Particles ± Other subst.++ Fat +	-	Prolapse of the cord
K 643/46	Particles ++ Other subst.+ Fat +	Amniotic fluid some- what discoloured	Strangulation by the cord. Adrenal hemorrhage
N 906/I/46	Particles ++ Other subst.++ Fat +		Prolapse of the cord

Number	Aspiration quantity	Intra-uterine asphyxia	Complications of labour Post mortem findings
K 3189/45	Particles + Other subst. +	Cardiac sounds ceased	Abruption of the pla- centa. Acute anemia
K 1811/45	Fat + Particles ± Other subst.+	_	of the fetus Prolapse of the cord Congenital microce-
N 979/I/46	Fat + Particles ± Other subst.+	_	phalus. Ecchymoses Pelvic presentation Ecchymoses
N 676/II/46	Fat ± Particles + Other subst. +	_	Rupture of the liver
K 1114/45	Fat +- Particles + Other subst.+	Discoloration of am- niotic fluid	Fetal hydrops.
N 2089/II/45	Fat + Particles ± Other subst. + Fat +		Face presentation. Subdural hemorrhag

made no attempt to classify on the tables substances which did not possess any definite form, instead of which I have used the general heading »other substances». The majority of them were seen as a precipitate; when stained with Weigerr's hematoxylin and VAN GIESON they took on a yellow or yellowish-grey colour, Dela-FIELD's hematoxylin and eosin produced rose, and Masson -- a purple staining. The elements did not as a rule take on mucicarmine, although bronchial glandular cells of the same section were stained an intense and clear red colour, - they can have had some fibre or particle staining red. In some cases the substance fully resembled the serum to be found in blood vessels, both with regard to staining and form. It is probable that this substance is mainly amniotic fluid, but one cannot with certainty distinguish it from edema fluid, although this latter is generally of a more homogeneous nature. It evidently depends on the protein contents of this substance, as to what an extent it becomes visible, which makes it clear that this amount also varies more in individual cases, than what whould be compatible with the aspiration occured.

There is one case in the group of asphyxiated who did not resuscitate (K 1114/45), who may have died from causes that had nothing to do with the delivery (Fetal hydrops). It was also noted in this case in the course of the delivery that the amniotic fluid was discoloured and therefore the moderate aspiration observed should still perhaps be considered greater than in a normal delivery. In the other three cases no mention is made of intra-uterine asphyxia. They had a small or medium amount of patches. The circumstance that these babies evidently died in consequence of the process of delivery makes it probable that factors influencing the aspiration have also been at work here.

It is therefore possible to say that one cannot, by examining the lungs of babies who died during pregnancy or delivery and of asphyxiated who did not resuscitate, get an idea of the amount of substances present in the lungs at the beginning of labour, not even of the state of things as they are when a normal delivery has come to an end. Only if the fetus had died without having had any possibility to aspirate, would it be possible to draw conclusions as to the *normal* amount of aspiration.

It is difficult to determine to what an extent the aspiration alone can be regarded as the cause of death of infants who died during pregnancy or delivery, or of asphyxiated who did not resuscitate. In order to consider the baby to have been suffocated by the amniotic fluid, it must be insisted upon that the autopsy should reveal signs of attempted respiration. Not a single case did show in the trachea or bronchi any such abundant amounts of aspirated substances, that they would justify a supposition of having fully obstructed a deeper penetration of the air. This being so, air must be found in the lungs as a mark of respiration, before it is possible to ascribe the suffocation to the liquor amnii. Otherwise the aspiration must be so strong that the amniotic fluid substances should entirely fill the lumina. Yet it is demonstrable that even in cases of a strong aspiration, the liquor amnii substances only fill part of the lumina (e.g. case K 643/46), part of them being air-containing. (Fig. 25) Moreover, in addition to a strong aspiration, the lungs have sometimes become aerated to a considerable degree, but the fetus had died nevertheless in the course of the delivery. (Case K 719/45). Although aspiration can have a share in the cause of death in these

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cases, the possibility must be taken into consideration that the deficiency in oxygen suffered by the fetus in consequence of compression of the cord, was an important factor, more important perhaps than the aspirated amniotic fluid.

Live-Born Fullterm Infants. — Particles of the amniotic fluid sunstances could be found in the lungs of all the live-born infants under 4 days old. (Table 12). The amounts were not especially abundant in any of these cases. Of the four who died in the course of the first 24 hours two had a medium and two small quantity of these particles. Only one of them was such as could be considered to have died of causes unconnected with the delivery (N 967/I/41). The autopsy revealed as cause of death a rightsided diaphragmatic hernia — the right lung was small — only about a quarter of the left. There was a small number of particles of the amniotic fluid and a medium quantity of fat and other (indeterminable) material. This case is the one of all four that most approaches the »normal» with regard to changes caused by the process of delivery. As there were malformations in the thoracic cavity which had an evidently impeding influence on the breathing, it can be supposed that the aspirated amount was next to the minimum quantity. In the other three cases there were factors that can be regarded as having caused the aspiration, and therefore they do not give any idea as to the amount of aspiration in a live-born »normal» infant.

It is to be taken into consideration already for infants who lived but a short time, but still more for those who survived for several days, that the amount of material to be found in the lungs is by no means the same as at the moment of birth. It is of course evident that the discharge of foreign substances from the lungs begins immediately after the onset of respiration. Even if the lungs retain some quantities of these substances, they cannot be considered to be equal to the amount at the moment of birth, nor is it possible to draw any conclusion on the basis of the remaining quantities, how much substance there was in each case at the moment of birth. Particles of the amniotic fluid were not to be found in my material in infants more than ten days old, and in one case (L 100/46) there were but isolated patches of epithelial cells and squamae from the skin of the fetus in an infant only two days old. No amniotic fluid

TABLE 12
Aspiration of Amniotic Fluid in Fullterm Infants under 4 Days old (Cases free from Membranes)

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Number, age	Aspirated quantity	Symptoms of asphyxia	Complication of labour Post mortem finding	
N 458/I/45	Particles +	Discloration of am-	Pelvic presentation	
18 min.	Other subst.+ Fat +	niotic fluid. Born as- phyxiated	Ecchymoses	
N 967/II/41	Particles ±	_	Diaphragmatic	
50 min.	Other subst. + Fat +		hernia	
K 1823/45	Particles ±	Discoloration of am-	Subdural hemorrhage	
3 ½ h.	Other subst.+ Fat ±	niotic fluid. Born as- phyxiated		
K 2399/45	Particles +	Born strongly as-	Transverse presen-	
12 h.	Other subst. + Fat ±	phyxiated	tation. Subdural he- morrhage	
N 2780/I/45	Particles ±	Fetal asphyxia	Prolonged labour.	
1 ½ days	Other subst.+ Fat ++	Born asphyxiated	Fracture of frontal bone. Subdural he- morrhage	
N 1255/II/45	Particles +	Born strongly as-	Congenital atresia	
2 days	Other subst.+	phyxiated	of the duodenum	
	Fat +		Diffuse peritonitis	
L 100/46	Particles ±		Congenital heart	
2 days	Other subst. ± Fat +		disease	
N 829/I/41	Particles +	_	Leptomeningeal	
2 days	Other subst. + Fat ++		hemorrhages	
N 845/II/46	Particles ±	Amniotic fluid grey?	Rupture of the liver	
2 days	Other subst. + Fat +			
K 862/45	Particles ±		Mors subita	
2 ½ days	Other subst.+			
P 358/45	Particles ± ?	?	Intraventricular he-	
3 days	Other subst. + Fat +		morrhage of the brain	

substances were found in the lungs of a seven days old baby (N 272/47), but another of the same age showed particles which reminded of the squamae found in the amniotic fluid (L 261/47).

Premature Infants

As there does not seem to be any considerable difference in the amounts of amniotic fluid aspirated by immatures and prematures, I have not considered it necessary to put them into different groups in this connection.

TABLE 13
Aspiration of Amniotic Fluid in Stillborn Premature Infants.

Number and birthweight	Aspirated quantity	Symptoms of asphyxia	Complications of labour Post mortem findings
K 591/45	Particles +	aroom.	Died during pregnan-
1930 gm	Other subst.+		cy. Congenital heart
	Fat ++		disease
N 352/II/45	Particles ++	_	Died during labour
1040 gm	Other subst.+		Ecchymoses
K 425/45 A	Particles ±	-	Hydramnion.
850 gm	Other subst. ±		Died during labour
	Fat ±		
K 425/45 B	Particles +		Hydramnion
670 gm	Other subst. ±		Died during labour
	Fat ±		Ecchymoses
N 1521/II/45	Particles +	No.	Eclampsism of preg-
2000 gm	Other subst. ±		nancy. Died during
	Fat +		labour. Leptomenin- geal hemorrhages
N 1027/II/41	Particles —?		Strongly asphyxia-
2220 gm	Other subst. ±		ted, not resuscitated
	Fat ±		

Table 13: The only fetus who had died during pregnancy had a medium quantity of liquor amnii particles. The cause of death was not revealed, as although Cor tricolulare was found at the post mortem it cannot of course be considered as the cause of death without any further question. Even if the cessation of the heart function is regarded as the cause of death, it must be still taken into consideration that respiratory movements could be made in that case at the moment of death. The delivery histories never made any mention of symptoms of intrauterine asphyxia in these cases. As the post mortem revealed positive findings in but

one case, and then only piarachnoid hemorrhages which are hardly adequate as a cause of death, — it seems advisable to consider as such in the first place trauma at the time of delivery, to which the delicate premature organism has succumbed. — Abundant aspiration was ascertained in one case only (N 352/II/45). Here the aspiration was so strong that the fetus might be considered to have been suffocated by the amniotic fluid, as the lungs showed that attempts at respiration had been made — some clearly extended lumina. The smallest amount of aspiration was found in the largest letus of the whole group. Some patches could be seen, which must probably be interpreted as squamae. The lungs were partly air-containing and they were affected with interstitial emphysema. Perhaps part of the substances in the lungs of this case may have disappeared but it is difficult to believe that great amounts should have disappeared in so short a time, if they had been originally abundant.

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In the lungs of stillborn premature infants the amount of aspirated amniotic fluid did not vary according to the weight at birth. It is not possible to prove, at least on the basis of these cases, that prematures with a lighter weight at birth aspirate less than those with a heavier weight. When comparing these cases to the corresponding group of fullterm infants, it seems that there is generally less amniotic fluid material in the lungs of premature than in those of fullterm babies.

TABLE 14

Aspiration of Amniotic Fluid in Live-Born Premature Infants under 10 days old (Cases free from Membranes)

Number,birth weight and age	Aspirated quantity	Symptoms of asphyxia	Complications of labour Post mortem finding	
N 788/I/45	Particles ±	_	Subdural hemorrhage	
1360 gm	Other subst. ±			
13 min.	Fat ±			
K 970/41	Particles ++		Diaphragmatic	
1480 gm	Other subst. +		hernia	
30 min.	Fat			
K 2621/45	Particles ±	Born slightly	Polycystic disease of	
2080 gm	Other subst.+	asphyxiated	kidneys	
30 min.	Fat ±			

Number,birth weight and age	Aspirated quantity	Symptoms of asphyxia	Complications of labour Post mortem findings
N 446/I/45	Particles ±	Born asphyxiated	Ecchymoses
1020 gm	Other subst. ±		
1 bour	Fat ±		,
N 852/I/45	Particles ++	Discoloration of am-	Ecchymoses
980 gm	Other subst. ±	niotic fluid. Born as-	,
2 hour	Fat +	phyxiated	
N 717/I/45	Particles ±		Leptomeningeal
2150 gm	Other subst. \pm		hemorrhages
9 ½ hours	Fat ±		
N 1043/I/41	Particles ±	Born asphyxiated	Subtentorial hemor-
1750 gm	Other subst.+		rhage
18 1/2 hours	Fat ±		
K 1019/45 A	Particles ±	Fetal asphyxia	Placenta praevia cen-
2430 gm	Other subst.+	Born slightly	tralis. Birth of twins.
22 hours	Fat ±	asphyxiated	Acute anemia of the fetus
L 26/46	Particles +	_	Subdural hemorrhage
970 gm	Other subst. +		
19 hours	Fat ±		
N 210/II/45	Particles ++	Born asphyxiated	Subdural hemorrhage
1240 gm	Other subst. ±		
23 hours	Fat ±		
L 129/47	Particles —	-	Pulmonary hemor-
2000 gm	Other subst.+		rhage
2 hours	Fat ±		
P 172/45	Particles ±	-	Leptomeningeal he-
1300 gm	Other subst. ±		morrhage. Icterus
4 days	Fat ±		neonatorum gravis
P 370/45	Particles ±		Subdural and intra-
1270 gm	Other subst. ±		ventricular hemor-
3 days	Fat ±		rhage
N 463/II/45	Particles ±?	Born slightly	Pelvic presentation
2180 gm	Other subst.+	asphyxiated	Subdural hemorrhage
6 days	Fat ±		
L 108/47	Particles ±	Born slightly	Purulent meningitis
1620 gm	Other subst. ±	asphyxiated	
7 days	Fat —		
P 76/45	Particles —?	-	Utero-placentar apo-
1300 gm	Other subst. ±		plexy. Congenital hy-
9 days	Fat ±		drocephalus. Serous peritionitis

Live-Born Premature Injants. -- (Table 14). Particles of the amniotic fluid could be found in the lungs of all who had succumbed within the first 24 hours. Three had an abundant, one a medium and six a samall amount. Strong aspiration was ascertained in the lungs of a premature baby who had survived for half an hour, although one lung was poorly developed, being only about one third of the other (K 970/41). The baby had a shallow breathing from the moment of birth. The cause of death was a large diaphragmatic hernia. Nothing is said as to the course of the delivery which might be taken as a cause of greater aspiration than usual. It can therefore be supposed that even such strong aspiration can occur without any special reason. When comparing this case to another with the same duration of life (K 2621/45), where the post mortem revaled a polycystic degeneration of the kidneys, a considerable difference is noted in the amount of aspiration. The cause of death in this case may be held a total lack of renal function, and the aspiration would then correspond to »normal». — In two cases with a strong aspiration the babies were asphyxiated at birth. In one (N 852/1/45) the aspirated substances were so abundant that they may be regarded to have suffocated the infant (Fig. 26). In the second case, on the other hand, (N 210/II/45) death was due to intracranial hemorrhage. Even in such a case where intra-uterine asphyxia was ascertained, there can be but little aspirated substances in the lung of a baby who survived for 22 hours. (K 1019/45 A.).

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If a comparison to fullterm infants is made, it appears that the amount of substances in lungs of premature babies who have died in the course of the first 24 hours, is about the same as in the fullterm. The comparison of the forementioned groups led to the idea that the premature, stillborn and asphyxiated who did not revive, generally had a smaller amount of aspiration than the fullterm. For both these observations to be in harmony with each other it must be supposed, that the disappearance of the amniotic fluid substances occurs more rapidly in the fullterm than in the premature, or that liveborn prematures aspirate as much as fullterm babies.

When making these comparisons it should be borne in mind that only such cases are reported here, where no membranes were found in the lungs. The formation of membranes in the prematures is exceedingly frequent during the first day of life (considerably more

than half of the live-born succumbed within the first 24 hours had membranes). It can be therefore supposed that just these cases who had a strong aspiration, were liable to be affected with membranes. As already said, I have not found it possible to determine the amount of aspirated amniotic fluid in cases with membrane formations, even to such an extent as was feasible where the cases free from membranes were concerned.

In a further examination of prematures with a longer duration of life, a baby two days old (L 129/47) already shows lungs microscopically free from liquor amnii substances. In this case the lumina were full of blood, and this is perhaps why no squamae and cells of the amniotic fluid could be found. In a baby 6 days old (N 463/II/45) only some patches were found, that were probably derived from the amniotic fluid. The particles found in the lungs of a case 9 days old (P 76/45) resembled as to their size the squamae of the liquor amnii, but their determination was uncertain. In prematures of this material I have found no more squamae of the amniotic fluid.

Since the material reported here is limited and it is difficult to conclude on this basis how frequently aspiration of liquor amnii takes place, I have endeavoured, by studying a more extensive material, to form on opinion as to the frequency of aspiration. With this aim in view, I have studied the material yielded by the post mortem examinations carried out by me, in addition to the material

TABLE 15

Aspiration of Amniotic Fluid in Infants who Died under 2 Weeks Age

Age	Number of cases	Amniotic fluid substances in alveoli	
o-2 days	Fullterm 46	46	
	Premature 52	51	
3-7 days	Fullterm 14	11	
	Premature 17	14	
8-14 days	Fullterm 10	4	
	Premature 5	4	
Total	144	130	

reported here. In part of that material specimens were taken only from one or two lobes, but sometimes pieces taken from all the lobes of the lung have been examined. The material thus obtained has been joined to that which is reported in more detail in this paper. (The cases with membranes are also comprised here). The results are illustrated by table 15. This table contains a great number of cases with sometimes very extensive inflammatory changes.

The Disappearance of the Amniotic Fluid Substances from the Lungs

On the basis of the above I have come to the conclusion that both fullterms and prematures have amniotic fluid substances in their lungs at birth. These substances can be found in the lungs of habies succcumbed in the course of the first week, but later they are found more seldom, and their amount is less.

The question therefore arises, by what ways the liquor amnii substances disappear from the lungs. It is difficult to elucidate it solely by means of post mortem material, as it is not known what was the position and the quantity of these substances in each individual case at the moment of birth. Still, I shall perhaps be able to report some circumstances throwing light upon this subject.

Squamae and Epithelial Cells in the Amniotic Fluid. — Not a single time have I been able to ascertain circumstances speaking on behalf of a disappearance of these particles by absorption. It can be seen in infants a week old that the squamae have changed their shape and are staining less well than in the lungs of babies sucsumbed in the course of the first 24 hours. As I have studied in this respect only cases free from inflammation, I am unable to say anything as to whether these substances dissolve or are absorbed in pneumonia. Since however they disappear from the lungs in all probability also without inflammatory processes, one easily believes the disappearance to take place in such a way, that the substances pass by respiratory passages into the mouth and from there into the alimentary canal. LEEGAARD has ascertained in his animal experiments that in rabbits the disappearance of iodipin injected into -the nether respiratory passages occurs chiefly by way of the trachea into the alimentary canal, and only a small part of it is absorbed

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by the lungs direct, which is a very slow process. These experiments support my supposition that the disappearance of the amniotic fluid substances happens through the trachea. With further reference to Leegaard's experiments, one may suppose that such a disappearance is due to ciliary motion, and also takes place without coughing.

Fat. — It is difficult to ascertain when the fat aspirated in the amniotic fluid disappears from the lungs. In fact, the babies often aspirate when sucking milk, and I find it is not always possible to discriminate between drops of fat due to this and fat from the amniotic fluid by means of a microscopic examination. It is however possible to study to a certain degree the appearance of fat outside of the lumina. In some cases drops of fat could be ascertained in the bronchial epithelium. (Fig. 27) They have been demonstrable both in fullterm and premature infants and could be found both in stillborn babies and such as had survived for a few days. If there is an abundant amount of drops, they appear in two rows, one of which is situated basally, and the other in close vicinity to the lumen. Sometimes there are more drops in the basal part than near the lumen. I have not ascertained any proportion between the fat in the lumina and in the bronchial epithelium. Fat was also present in the connective tissue surrounding the bronchioli. On the basis of observations it is hardly possible to maintain, or at least consider it as proved that these findings speak on behalf of a absorption of fat by way of the bronchial epithelium. -- In some cases the capillary serum in the lungs was stained yellow by sudan. Sometimes the contents of larger vessels, when stained with sudan or scharlach-R, were of a paler yellow than the contents of capillaries touching them. I feel that such observations support the theory that fat can be directly absorbed into the blood. It seems possible that part of the fat disappears by way of the trachea.

It was not generally possible to establish with any certainty in the sections that the drops of fat or the squamae from the amniotic fluid disappearing from the lungs were amassed in the bronchioli. In case N 352/II/45 on abundant amount of liquor amnii squamae and cells was clearly visible in the »bronchioli», and the corresponding peripheric area contained only precipitate. (Fig. 28) Another place had a similar aspect, the difference consisting in a lack of

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contents in the peripheric lumina. In other places of the same section there were unmistakable squamae and cells from the amniotic fluid also in the lumina of the peripheric parts. These observations speak on behalf of the supposition that the substances were withdrawing through the bronchioli after the expansion of the lumina. Such histologic aspets in the section need an abundant amount of amniotic fluid. If the disappearance is slow and the quantities of amniotic fluid small, such forms do not spring into existence, even if the disappearance takes place through the trachea. Consequently, the absence of such observations does not war against my supposition.

Nothing can be said of the disappearance of other substances on the basis of the sections. The precipitate mentioned above probably strongly recedes already after the first few inhalations, so that the same subject can have unmistakably less of it in the extended alveoli than in the smaller »flabby-walled» areas. It does not seem impossible that this substance is absorbed in considerable quantities, but it is evident that it also diseappears throught the effect of respiratory movements. As it is not fully certain whether this substance at all belongs to the amniotic fluid, I feel there is no reason to take up a study of its disappearance.

Taking the amniotic fluid substances together, it can be said of their disappearance that even if part of them are absorbed directly by the lungs, they probably vanish mainly the tracheal way. This theory is further supported by the observation that breathing of even a short duration achieves a great decrease in the amount of the liquor amnii substances — also in such cases where part of the lung is aerated and part has remained congenitally atelectatic. This is especially the case in subjects in whom part of the areas has becom "fully" aerated, and part has remained equally "fully" atelectatic.

Often large cells could be found in the lumen that contained drops of fat and resembled in shape alveolar epithelial cells. The finding of these cells and the circumstance that they contain fat drops does not prove that their fat is a phagocytic one from the amniotic fluid. When performing autopsies I have found in such pulmonary tissue that was entirely unconnected with the lung themselves, a great quantity of cells of the forementioned appearance in the lumen, containing drops which were stained red by sudan (Case L 35/47). It cannot be maintained that in this sub-

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By who o thems did n ject who was 9 months old, the fat originated from the aspirated amniotic fluid, but it must have come into the cells from other sources. — I do not want to assert on this basis that the alveolar phagocytes should be unable partly to take fat, but to my mind the case clearly proves that there is no need to consider such an occureence as absolutely certain, even if one does find in the lumina fat-containing cells.

Cases Containing Membranes

My material comprises in all 30 cases affected with membranes. With the exception of two cases membranes appeared in infants who survived for less than a week.

TABLE 16

Membranes in Live-Born Infants who Died under 7 Days Age

	Total number	Membranes
Fullterm	18	6
Premature	34	19
Total	52	25

Table 16 illustrates the occurence of membranes in non-inflamed lungs of live-born infants who had died under a week old. As shown by the table, there is a difference between premature and fullterm babies in the frequency of the occurence of membranes. A difference can also be ascertained in the morphology of the membranes. It is therefore advisable to make a separate report on the fullterm and the premature when dealing with the appearance of membranes.

Fullterm Infants

By means of staining fat it was possible to ascertain in a case who died in the process of delivery, that the fat drops had aligned themselves along the walls (Case N 810/II/45). The paraffin section did not reveal any membranelike formations. I do not feel this

could be interpreted as a membrane formation in the same sense as represented below and reported in literature. One baby who had died during delivery had a small amount of membranes (Case N 906/I/46). It was clearly visible how they had originated from squamae. There were also unmistakable transitional forms between the membranes the squamae amassed at the walls. However, it was always possible to distinguish in membranes a distinct lamellar structure - i.e. there were no membranes of a homogeneous substance. The lungs were macrosopically air-containing and the microscopic examination revealed extended tense lumina, which had clearly become aerated. Membranes were found only on the walls of these extended lumina. Another subject who died in the course of the delivery (K 643/45) showed liquor amnii squamae disposed in lamellae along the walls of unmistakably extended lumina. (Fig. 25) This case should be considered an intermediate form of cases with and withbout membranes.

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The youngest of the live-born infants in whom membranes were ascertained died not quite five hours old (N 350/I/46). The lumina generally had a small amount of epithelial cells and squamae of the amniotic fluid. Medium quantities of a precipitated substance were revealed by the paraffin section, and fat staining (sudan) showed a moderate amount of fat in the lumina. In some of them a precipitate was found plastered against the wall, where sometimes a dark particle of the size of an alveolar epithelial cell nucleus could be seen, but no other particles. These formations followed the course of the lumen contours, often closely adhering to the walls Their thickness varied. Sometimes a bronchiolus was completely obstructed by this material. These formations could not be found in all the lumina, even the most extended, and in some sections they were only seen here and there on the whole area of the section. There were more of them in sections taken from the left lung, and in the area of the left lower lobe they could be seen in every field. Sudan stained the membranes an orange colour. Membranes were present in the areas of some bronchioli, but the largest quantities were found to the periphery of bronchioli, although not quite in the outermost parts.

Since the mother was affected with diabetes, it is possible that convulsions and cyanosis, as well as accelerated breathing of this baby were due to hypoglycemia. It appears most probable that hypoglycemia was the reason of the fits described, and the membranes as such did not play any important part as a cause of the primary respiratory disturbances. The amount of membranes was so small that they cannot be considered as a cause of death. At the utmost, they may have been a contributory factor.

Case N 589/II/46 was delivered by a cesarean section and a considerable amount of amniotic fluid was discharged through the mouth after birth. The post mortem revealed a foaming substance in the trachea and its principal ramifications. Macroscopically the aeration of the lungs was scarse and microscopically too, only a few lumina were extended and air-containing. It could be distinctly seen in some places how the precipitate, which stained a pale colour, collapsed against the walls forming membranes. These were nearly homogeneous and contained abundant quantities of fat. They did not show anywhere squamae of the amniotic fluid or other particles. Squamae or epithelial cells of the amniotic fluid were not found in the lumina either. There were in some bronchioli cellular masses staining a dark colour, which seemed to be detached bronchial epithelial cells.

It is difficult to determine in such a case whether the membrane-forming substance in the lumina is aspirated amniotic fluid. The squamae having been so scarse, there is nothing to expose the substance with certainty as amniotic fluid (see above p. 71). The abundant aspiration of amniotic fluid at the moment of birth speaks for the supposition that the substance was amniotic fluid. In this case the blood serum looked the same in microscopic sections as the abovementioned precipitated substance, therefore it cannot be decided on the basis of the histologic preparation that the substance was aspirated amniotic fluid. — Yet taking into consideration the clinical findings, this appears highly probable.

The contents in case N 494/II/45 were both a precipitated substance, as well as skin squamae and epithelial cells. Both were also present as membrane substances. Homogeneous membranes were found, the shape of which did not give any indication as to their origin. (Fig. 29) Membranes abunded in all the specimens, and could also be seen in narrow lumina. There were none in the bron-

chioli, but only to the periphery of these — being present $even\ in$ the most peripheric parts (See Fig. 15)

Case N 832/II/41 had membranes in several places, mainly in the bronchioli area, but membranes could also be seen in more peripheric parts. The lumina were often full of blood. The origin of the membrane substances could not be ascertained in this case. There were no amniotic fluid substances in the membranes, nor could their presence be established with certainty in any part of the lengs. In some places a few granulocytes could be found in the lumina.

The presentation of this case in the group of subjects free from infection may be erroneous. The possibility must be taken into consideration that the hemorrhages were due to infection. The findings of small quantities of inflammatory cells support this possibility. However, as there were no evident inflammatory symptoms, I have considered the inclusion of this case justified. The microscopic findings in case N 768/I/41 were similar to those of N 832/II/41, some isolated squamae of the amniotic fluid were present in the lumina.

I cannot consider it fully proved that the membranes had the same origin in these cases as in the others. This circumstance is not demonstrable morphologically, as it is not possible to ascertain that membranes are formed by substances in the lumen originated from the amniotic fluid. This is not supported by the fat contents of the membranes, as in cases reported in literature there has been fat in the membranes, in spite of the circumstance that they had been found in adults or so much older children, that there could not be any amniotic fluid substances in the lungs. If however one compares these membranes to those reported in other cases and finds that they greatly resemble each other, it seems probable — when taking the infant's age into consideration — that they have originated from liquor amnii substances also in this case.

Case P 276/45 resembles the two last mentioned. (Fig. 30) This subject had a great amount of membranes, and the lumina were full of erythrocytes. The membranes were thick, rather homogeneous and turned yellow when stained with sudan. They were clearly distinguishable from the tissue below. There were some cells in them, but no particles. Unquestionable amoiotic fluid substances were not found anywhere in the lungs. Among the erythrocytes in

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the lumen there were a few granulocytes, but no accumulations of them could be ascertained. The lungs had but a few aerated areas. The membranes extended from the bronchi nearly to the outermost periphery. They showed in some places layers of lamellae, and here and there it seemed as if additional substances were accumulating on the membranes. — Also such lumina as were free from membranes, were full of erythrocytes.

Thus, the case is similar to the two previous cases as to the microscopic aspect, but its changes are much more strongly developed. The infant had survived for 13 days and the symptoms had persisted for 11 days. The principal symptom was dyspnea which became gradually worse -- finally leading to death. The onset of symptoms so soon after birth and the extension of the microscopically found changes, which is compatible with the supposition that the formation of membranes began simultaneously with the onset of the symptoms, - bring this case into close relation with those, where the substances of the amniotic fluid had formed membranes. It cannot be expected that liquor amnii substances should still be demonstrable in the membranes, even if they had originally been a membrane-forming factor. Although it is supposed that amniotic fluid substances have formed the first membranes, this does not exclude the possibility of a later appearance in the membranes of additional substances, not that new membranes might have originated from these substances.

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The character of other fullterm cases with membranes is made evident by table 17.

Premature Infants

In my material membranes in premature subjects were only found in those under 6 days old — they were especially frequent in babies succumbed during the first 24 hours. They did not greatly differ as to structure from the above reported cases. Yet they present some features which are perhaps more characteristic of membrane formations in the lungs of premature than in those of fullterm infants

Not a single time could membranes be ascertained in the lungs of stillborn premature infants. There is one case among the asphyxiated who did not resuscitate, that had membranes (case N 1618/

TABLE 17
Membrane Substances in Fullterm Infants

Number	Liquor amnii squamae and cells	Precipitate	Bronchial or alveolar cells	Indeterminab le substances
N 906/I/46 A	+	±	_	
N 350/I/46	+	+	_	
N 589/II/46	+	+	-	
K 965/46		+	-	
L 188/47				+
N 494/II/45	+	-		+
N 832/II/41	_			+
N 768/I/41	_		-	+
P 276/46				+

TABLE 18
Membrane Substances in Premature Infants

Number	Liquor amnii squamae and cells	Precipitate	Bronchial or alveolar cells	Indeterminab le substances
N 2663/II/45 A	_	±	+	_
N 2663/II/45 B	+	+ ?	+	±
N 930/I/45 B	+	+	+?	+
N 505/I/45	+	_	++	+
N 531/II/45	+	_	+	_
K 423/45 B	±	•	土	土
K 2188/46 B	±	土	土	士
N 223/II/45	土	-		士
L 162/47			+	+
K 602/46	+	+	± ?	+
L 33/47	-	_	_	. +
N 519/II/46 A	+	-	· ±	+
N 519/II/46 B	+		±	-
N 519/II/46 C	+	+	_	-
L 94/46	+	+	+	_
L 95/46	+	+	+	+
K 720/45	+	-	+	-
N 575/II/46	+	?	士?	+
N 935/I/45	+	_	_	_
P 203/45	-	-	_	+
N 1618/I/45 B	+	+		+

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one peri I/45 B, weight at birth 2.360 g.). Macroscopically no aeration could be found in the lungs. In the microscopic section there were unmistakably tense walls that resembled lumina of fully air-containing lungs. These were not seen however in the most peripheric parts. Membranes were abundant and partly formed of a precipitated mass. Amniotic fluid squamae and cells were rare in them. They were found in the tense walls, but also in somewhat more narrow only partly extended lumina could membranes frequently be seen. Blood was abundant in the lumina, and in some places the membranes contained red blood corpuscles.

Two pairs of twins belonging to the group of liveborn prematures had membranes. In addition, there is a set of triplets who all had membranes. Neither of the twins N 2663/I/45 were in a good condition after birth, but the A-baby was worse than the B-baby, and he died sooner than the latter.

The A-baby had a weight of 1.310 gm. at birth and he lived for an hour. The B-baby weighed 1.470 gm. and survived for 14 hours. Leptomeningeal edema was revealed by the post mortem in both cases, but nothing else of interest. The aeration was poor in the lungs of both subjects - B-baby had macroscopically and microscopically more air-containing areas than the A-baby. The latter had a lesser quantity of pulmonary capillaries and a greater amount of cells in the lining than the B-baby. Both had membranes. In A-baby they were present in extended »bronchioli» with tense walls. There were also such »bronchioli» where no membranes were found in the lumina. The substance of the membranes was a precipitate and particles which took on a dark colour when stained and evidently were pyknotic nuclei. (See Fig. 31) (See also Table 18). This mass was also loose in such places of the lumen, where it was small and the wall »flabby». These cells were clearly originated from alveolar lining cells, as intermediate forms could easily be ascertained in them. There were very small quantities of amniotic fluid substances -- only some isolated cells of the skin epithelium. The fat staining revealed that the membranes and the said cellular mass were fat-containing. The »bronchial» epithelium had an abundant amount of drops stained red with sudan, arranged in two layers, one at the base and the other in the vicinity of the lumen. More peripherically than these, no fat could be found in the cells.

The B-baby had more amniotic fluid substances in the lungs than the A-baby, although he neither had an abundant amount. Membranes were somewhat more frequent here and their composition was the same as above. Yet some places showed forms which make it probable that membranes are formed by the epithelial cells and squamae of the amniotic fluid — it also seemed that these could produce masses of the same character as described above, perhaps from the proper cells of the lungs. Tinctorially the membranes were strongly fat-containing and there seemed to be some squamae-like particles. There was only a scarse quantity of fat drops in the *bronchial* epithelium and their distribution was irregular. Only part of the extended lumina had membranes. Some of them were such membranes, that their origin could not possibly be determined, as they did not show any separate parts, consisting of a smooth fine-grained substance. These membranes were also fat-containing tinctorially.

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The immature twins L 94/46 and L 95/46 both survived for an approximately equally long time (about 7 h.) and both had impeded breathing. Macroscopically the post mortem did not reveal anything but leptomeningeal edema. The lungs of both were only partly aircontaining. Microscopically both subjects had a poor aeration, yet it was more extensive in L 95/46 than in its twin. The greater aeration was accompanied by a smaller amount of amniotic fluid substances and simultaneously, less membranes. The difference was not considerable, yet clearly visible. L 94/46 had membranes chiefly on the walls of the tense lumina, but they could be ascertained also on some small lumina with »flabby» walls. The membranes were located in the parts to the immediate periphery of the »bronchioli». (Fig. 32) There were none in the pneumonomeres, nor in the »bronchioli» area. The membranes consisted of the same masses with dark particles as have been described above — it appeared as if these masses were in some places originated by cells which had come off the walls. On the other hand it seemed clear that also the amniotic fluid squamae were plastered against the walls, forming membranes. The membranes were unmistakably fat-containing, with a considerable amount of drops staining yellow with sudan. By means of this staining the membranes stood out clearly from their surroundings, as the other tissues did not contain substances responsive to sudan. The bronchial epithelium was free from fat.

 $\rm In~L~95/46$ the membranes were distributed in the same way as in his twin. Morphologically and tinctorially they were also of a similar character. It seemed quite evident that the membrane-forming mass had originated from the liquor amnii squamae, as well as from pulmonary epithelial cells that had become detached.

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The weight at birth and age of the triplets N 519/II/46 were as follows:

	Weight at birth	Age
A	1.310 gm.	14 hours
B	1.150 gm.	14 1/2 ,,
C	1.080 gm.	29 ,,

It was evident that the C-subject, who survived longest, had the smallest amount of membranes. There were only short bits remaining, which were fat-containing. The membranes consisted, at least mainly, of amniotic fluid squamae and epithelial cells. These substances were also in the centre of the lumen, without having become plastered against the walls. For the main part, the lumina were empty and free from membranes. The A- and B-subjects had more membranes than C. B had most. In both of them the membranes were formed from the squamae of the amniotic fluid, but also epithelial cells that had come off the walls could be found, and they formed the above described mass containing dark particles, being in this way a contributory factor in the origination of the membranes. The position of the membranes in all three subjects was the same as described above for cases L 94/46 and L 95/46.

The C-case had an unmistakably greater aeration than A and B. (See Fig. 33, 34, 35)

Membrane Substances and Position

Fat was a constant finding in the membranes, (Fig. 36) it stained red with sudan and scharlach-R, but Nile blue sulphate had no effect on it, or produced only a pale blue colour. In all cases the Liebermann-Burchard-Schultze reaction was negative in the membrane substances. Not in any single case did they become stained by mucicarmine, at the utmost the edges took on a reddish stain. The maximum effect produced by thionin was a bluish tint

— no metachromic staining could be ascertained. The membranes did not stain in the same way as fibrin, nor was any fibrin-like structure visible in them. Bauer's polysaccharides reaction was negative. The membranes stained yellow with Weigert's hematoxylin and van Gieson — being sometimes of a homogeneous smooth substance, sometimes on the other hand, lamellae and darker particles could be distinguished. They stained a reddish-purple with Delafield's haematoxylin and eosin. When stained with Masson's acid fuchsin-aniline blue they took on a strong bluish-purple colour. The membranes were best revealed in the sudanorange or scharlach-R stainings, as they were then clearly distinguishable from their surroundings — but they were also visible in paraffin sections in all the staining methods employed by me.

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When examining membranes, parts are often found, which in all probability have their origin in the detached and partly disintegrated bronchial or alveolar epithelial cells (Fig. 31 Table 17, 18)*) Moreover, substances of the amniotic fluid were of a frequent occurrence. (See Fig. 25.) In addition, there are membranes whose substances it is not possible to specify, owing to the circumstance that they are of a homogeneous or slightly granular nature, where the ingredients cannot be determined with any exactness on the basis of their form and staining (Fig. 29, 30, 37.) — Sometimes the membranes are entirely or partly formed from a precipitated substance. This substance was in fact constantly found in considerable amounts in the lungs of stillborn babies, and its character has already been described. It cannot be distinguished from the blood serum, either morphologically or tinctorially. On the basis of my material I maintain that it is, at least partly, a liquor amnii substance. (See case N 589/II/46 pag 85).

When examining the membrane substances in my cases, it seems that the substance forming them originates from the amniotic fluid, or from detached alveolar or bronchial cells. The fat contents of the membranes do not allow of any conclusions as to their origin. In fact, there are fat-containing substances in the amniotic fluid, but the abovementioned cells also contain a substance staining in

^{*)} In this table the membrane substances are regarded as being alveolar or bronchial epithelium cells only if intermediate forms were present, as explained in the cases reported above.

the same way, which also appears in small drops. There are fat drops in the bronchial epithelium, also in such cases where no loosening or disintegration can be established. Thus, the presence of fat is no help for drawing conclusions as to the origin of membranes. As described in the above cases, it can be seen in the sections how the liquor amnii squamae become plastered against the walls as a membrane. (See Fig. 25.) There are also membranes where the squamae and cells of the amniotic fluid do not have an equally visible shape, but they can still be recognised. It is probable that the disintegration of these substance has altered their shape and one can suppose that this process continues, so that the membranes become homogeneous or nearly so. It is possible in the same way to distinguish intermediate forms between the bronchial epithelial cells and the membranes. When the membranes assume their definite shape, it is often difficult to recognise their origin. Thus, there is the possibility that membranes can be formed by some other substances, besides the abovenamed. I have been unable to determine this with the help of histologic sections. It was moreover impossible to say whether the membranes receive additional substances, e.g. from the blood circulation — but on the other hand, this possibility cannot be excluded on the basis of studies of the sections.

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I have found membranes only in such lungs, where respiration had occurred. In them the membranes have placed themselves along the walls of extended tense lumina. Yet they have also been found on such walls of the air-spaces, where the lumen was small an the wall tourtuous. This was found also in the lungs of asphyxiated infants who did not resuscitate. The lumina of these subjects were unmistakably more extended than those found in the lungs of stillborn babies, and the extension of the lumina varies — a mark, on the basis of which I have endeavoured to differentiate between congenital and secondary atelectasis. There were never any membranes in such sections that did not have any unmistakably aircontaining areas. - Sometimes membranes also occured in quite narrow lumina (case N 494/II/45), but it is to be surmised that these lumina have collapsed, either intra vitam or postmortally. (Fig. 15.) It must in general be taken into consideration that even if membranes are found in lumina with tortuous walls, the possibility exists that this tortuousness is due to the collapse of the lung after death. Membranes have been found in the bronchi and bronchioli, and also in the most peripheral parts of the alveolar tree, but they were most frequent, both in fullterm and premature infants, in the areas which lie to the periphery of the bronchioli — but at the outermost periphery (in the alveoli, »Endknospen») they are both rare and scarse. In the prematures, membranes appear just in such pulmonary parts, which have the most extended lumina and tensest walls, and which have the greatest number of capillaries. There were considerable variations in the number of membranes in individual cases. In my material I have also placed such cases into the membrane group, where only a few of them could be ascertained in one single section. In places the membrane was unmistakably coming off the wall and their quantity was insignificant everywhere.

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The Relation between Respiratory Disorders and Membranes and their Manner of Origin.

Mention is made in the survey of literature that Farber and Wilson have experimentally ascertained the formation of membranes to be due to forced respiration. It is therefore advisable to examine, to what an extent respiratory disturbances in cases affected with membranes can be ascertained in my material. Information gathered from delivery reports is not always a suitable base for accurate knowledge in this respect about every individual case, as the annotations about the condition of the child are often very short and summary, and in some reports they are restricted to a description of the state immediately after delivery. But part of the reports give minute descriptions of the infant's state. Tables 19, 20 present the respiratory disturbances ascertained on the basis of delivery reports and case histories. The same table also illustrates the post mortem findings and the probable cause of death.

In the fullterm group five subjects had considerable disorders of breathing, which are mentioned in the delivery reports or case histories. Of these five no other cause of accelerated respiration could be found in two cases (N 589/II/46 and P 276/46) than membranes. In the former, membranes were formed of a substance which morphologically could not be indisputably proved as having ori-

TABLE 19
Fullterm Infants Containing Membranes

Number	Respiratory disturbances	Other post mortem findings	Cause of death
N 906/1/46 A		Leptomeningeal edema. Adrenal hemorrhage. Renal hyperemia	Adrenal hemorrhage. Died during labour
N 350/I/46	+	_	Hypoglycemia?
N 589/II/46	+	Leptomeningeal edema.	Aspiration of amniotic fluid?
K 965/46	-	Rupture of tentorium ce- rebelli. Subdural hemor- rhage. Congenital hydro- nephrosis	Intra partum lesion
L 188/47	+	Leptomeningeal edema	Hypoglycemia?
N 494/II/45	_	Congenital hydrocepha- lus. Congenital heart di- sease	Congenital heart disease
N 832/II/41	?	Leptomeningeal edema	Vernix membrane
N 768/I/41	?	Universal jaundice Adrenal hemorrhage	Icterus gravis neonato- rum. Adrenal hemor- rhage
P 276/46	+	_	Vernix membrane

ginated from the amniotic fluid, although this seemed probable. In the second case, the character of the membrane substances was morphologically still more uncertain, the baby having survived for such a long time that even had the substances come from the amniotic fluid, it appears improbable that these substances could still be demonstrable. Two cases probably had hypoglycemia, which can be thought to have brought about changes in the respiratory activity — and it can thus be considered that in these cases an extrapulmonary cause had provoked the quickened breathing necessary for the formation of membranes — if we think along the lines of of the abovementioned experiments. In the fifth case (N 906/I/46 A) disorders of breathing can be regarded as due to a complication in the process of delivery — (prolapse of the cord) — the child died during labour. In four cases, where the reports do not make any mention of respiratory disorders, the post mortem revealed in three

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TABLE 20
Premature (and Immature) Infants Containing Membranes

Number	Respiratory disturbances	Other post mortem findings	Cause of death
N 1618/I/45 B	_	Leptomeningeal hypere- mia. Hyperemia of liver and kidneys. Subepicard- ial ecchymoses	piration of amniotic fluid
K 720/45	?		Congenital debility
N 575/II/46	+ .	Leptomeningeal and in- traventricular hemor- rhage	
N 935/I/45	+?	Leptomeningeal hemor- rhage	Congenital debility Intra partum lesion
P 203/45	+	. —	?
L 94/46	+	Leptomeningeal edema	Vernix membrane
L 95/46	+	Leptomeningeal edema	Vernix membrane
N 519/II/46 A	+	Intraventricular hemor-	Intra partum lesion and
N 519/II/46 B N 519/II/46 C	+ +	rhage of brain. Leptome- ningeal hemorrhage of medulla oblongata. Lep- tomeningeal edema Leptomeningeal edema Intraventricular hemor- rhage of brain. Leptome- ningeal hemorrhage of medulla oblongata. Lep- tomeningeal edema	Vernix membrane Vernix membrane Intra portum lesion and vernix membrane
N 2663/I/45 A	+?	Leptomeningeal edema	Vernix membrane
N 2663/I/45 B	+?	Leptomeningeal edema	Vernix membrane
N 930/I/45 B	+	Rupture of the liver Hemoperitoneum	Rupture of the liver
N 505/I/45	+	Subdural hemorrhage	Intra partum lesion
N 531/II/46	+	Leptomeningeal edema	Intra partum lesion
K 423/45 B	+?	Serous peritonitis Adrenal hemorrhage	Peritonitis
K 2188/46 B	+	Subdural hemorrhage Subepicardial and thy- mic ecchymoses	Intra partum lesion
N 223/II/45	+		Intra partum lesion and vernix membrane

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Number	Respiratory disturbances	Other post mortem findings	Cause of death		
L 162/47	+	Subdural hemorrhage of spinal cord. Leptomenin- geal edema	Intra partum lesion		
K 602/46	+?	Subdural hemorrhage. Subepicardial and mediastinal ecchymoses	Intra partum lesion		
L 33/47	+	Leptomeningeal edema	Septicemia?		

diseases which can be supposed to have caused respiratory changes, while one case (N 832/II/41) remained unsolved in this respect.

It therefore seems the material tends to prove that in fullterm infants causes often can be found outside of the lungs which may be taken to have provoked quickened breathing, thereby being partly responsible for the formation of membranes. Yet there are cases where no such factors can be disclosed, but the membranes as such have caused the quickened breathing. One sometimes finds in these cases that the difficulties of breathing have set in immediately after birth, and difficult labour must then be considered as having originated the formation of membranes.

In premature infants difficult breathing was observed in the majority of cases with certainty and in the rest with probability. When basing the estimation on the post mortem findings, a great number of cases in this group are such, where no extra-pulmonary factors are revealed that could be regarded as a cause of respiratory changes. The material comprises six cases, in which a macroscopic examination did not reveal anything besides leptomeningeal edema. In addition to them, there were three in which the post mortem examination did not disclose anything of a pathologic nature, besides the pulmonary findings. We must place into the same group the ease where nothing was found, in addition to hyperemia of the tissues (N 1618/I/45 B). The disorders of breathing in this case can however be ascribed to circumstances provoked by the process of labour, as the baby died in the course of it. Merely the occurence of pia-arachnoid hemorrhages in the vertex can hardly be considered a significant factor in the origination of quickened breathing (N 935/I/45). In the three remaining cases hemorrhages were found in the region of the medulla oblongata or in the area of the spinal cord, and these lesions can be regarded as having a significant influence on the respiration. Subdural or intraventricular hemorrhages can also be regarded as such, and they were found in six cases in all. One subject had peritonitis, one rupture of the liver, and one probably sepsis, which can all be factors causing respiratory changes.

It can therefore be said that in about half of the cases of this group quickened breathing was caused by factores outside the pulmonary area, but in the other half no extrapulmonary causes of respiratory changes can be ascertained.

Irregular breathing is found so often in premature infants, that it can be regarded as a constant phenomenon in them, without any other anatomic findings but underdevelopment. The membrane substances in the prematures were of a partly different character than in fullterm babies. In the prematures, one can frequently find membrane substances formed by detached pulmonary epithelial cells, whereas this was not demonstrable in fullterm infants; the question therefore arises whether the tissue changes, due to a premature functioning of the lungs in the former group, have a significant influence on the appearance of membranes. It seems as if, with the onset of respiration, there is a loosening of epithelial cells, both in the central and the peripheral parts of the premature lungs. In all probability, the cell masses, thus detached, take a part in the formation of membranes. When comparing the tissue structure of an immature baby immediately after birth to the lungs of one aged 5 days, it seems that the subject with a longer survival has a considerably smaller amount of alveolar epithelial cells. It is therefore possible that a detachment of cells has taken place here — the mass formed in this way can be supposed to be a causative factor of difficult breathing. Respiratory disturbances can then appear, under the influence of which the substances are plastered against the walls, and membranes originate. In my material immatures are more often affected with membranes than prematures, which speaks on behalf of the theory of their appearance in the prematures and immatures. It is impossible to prove this contention on the basis of the material - and it must be admitted that it has its weaknesses. This loosening of the cells alone does not explain the

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appearance of membranes, but I feel it must be taken into consideration as a contributory factor, especially for the immatures.

TABLE 21
Aeration of Lungs in Fullterm Infants Affected with Membranes

No birth weight and age		I	1	11		III		IV		V	
	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Remarks
N 906/1/46 A died during labour	+	-	±	_	±		±	-	±		Ample quant. squa- mae and precipitate. Moderate quant. membranes.
N 350/I/46 4 ½ hours	++	-	++	-	++	-	++		++	-	Moderate quant. li- quor amnii particles and precipitateSmall quant, membranes.
N 589/II/46 7 ½ hours	++	-	++	-	++	-	++	-	++	-	Precipitate abundant, particles very scarse.
K 965/46 9 hours	++	-	++	-	++	-	++		++	-	Precipitate abun- dant, liquor amnii particles scarse, mo- derate quant. mem- branes.
L 188/47 14 hours	± ?	±	-	+	±	±	±	±	±	土	Moderate quantity membranes. Blood in lumina, small quant. squame.
N 494/II/45 1 day	±	+	+	±	土	±	土	+	土	±	Abundant quant. Abundant quant quor amnii particles and membranes.
N 832/II/41 5 days											Blood abundant in lumina. Membranes only in bronchi.
N 768/I/41 8 days											Blood abundant in lumina.
P 276/46 13 days											Lumina full of blood Very abundant quant. membranes.

Signs: — no atelectatic areas, \pm small atelectatic areas, + middle sizes atelectatic areas which do not comprise half of the area of specimen, ++ atelectatic areas being half or more of the area of specimen.

G = congenital atelectasis, G = secondary atelectasis. I = right upper lobe, II = right middle lobe, III = right lower lobe, IV = left upper lobe, V = left lower lobe.

Tables 21, 22 illustrate the aeration of the lungs containing membranes. (I have used the same basis of estimation as in tables 7, 10 for the aeration of lungs free from membranes). On these grounds, it is not possible to draw many conclusions as to what an extent the membranes prevent the aeration of the lungs. When

making a comparison with the cases free from membranes, it seems that the aeration was slower in fullterm subjects who had membranes. It is even more difficult to make the comparison for the prematures, nor is there any clearly marked distinction between lungs free from membranes and lungs affected with them. When studying the sections, it can often be found how a membrane seems to obstruct the space between an extended lumen and a narrow one continued from it, — thus it would prevent the aeration of the peripheral part. However, one can also see lumina extended in this way in cases, where no formations of membranes are revealed.

TABLE 22

Aeration of Lungs in Premature Infants Affected with Membranes

No. birth- weight and age	I		I	II		III		IV		7	Remarks
	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Acting as
N 2663/I/45 A 1310 gm	++	-	++	-	++	_	++	_	++	-	Small quant, membre small quant, liquo amnii, particles.
1 hour N 2663/I/45 B 1470 gm	++		++	-	++	± ?	++	±	++	±	Small quant, mem bran, but more that in preceding, lique
14 hours N 930/I/45 B 2220 gm	±	±	+	+	+	+	+	+	+	+	amnii particles like wise. Moderate quanti membranes, also am niotic fluid. Severa alveoli full of nearly
3 hours N 505/I/45 1520 gm	土	+	_	++	± ?	+	_	++	+	+	homogeneous sub stance. Moderate quant. membr., liquor amu particles scarse. Pre
3 ½ hours N 531/II/46 1560 gm	+	+	+	+	+	+	+	+	±	+	cipitate in seven places. Membranes are sca se, liquor annii pa ticles likewise. Mode
4 hours K 423/45 B 2050 gm	±	±	±	±	+	+	土	±	+	+	rate quant, precip tate. Membranes are sea se. Amniotic flu substances likewise
4 ½ hour K 2188/46 B 2100 gm	±	±	±	±	土	±	±	土	土	+	Ample quant, mer branes, small quar liquor amnii parti
5 ½ hours N 223/II/45 2270 gm 8 hours	-		-	土	_	+	_	土	±	±	les. Precipitate several places. Membranes are sea se, moderate quan liq. amnii particle

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L 162 1780 12 ho K 602 2420 21 ½ L 33

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No. birth- weight and age	1	1		II		III		IV		7	D
	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Ca	Sa	Remarks
L 162/47 1780 gm	±	+	±	±	土	±	±	±	土	+	Membranes are scar- se, liq. amnii partic- les likewise. Small quant. precipitate.
K 602/46 2420 gm 21 ½ hours	± ?	± ?	+	±	±	+	+	+	±	+	Moderate quant. membr. small quant. liq. amnii particles. Ampre quant. preci-
L 33/47 1380 gm	_	士	_	_	±	+	土	±	±	土	pitate. Membranes very scarse some isolated particles of liq. am- nii. Lumina full of
5 days N 1618/I/45 B 2360 gm Asphyxiated, not resuscita- ted	++	_	++	_	++	-	++	_	++	_	

Signs: Ca = congenital atelectasis, Sa = secondary atelectasis. I = right upper lobe, II = right middle lobe, III = right lower lobe, IV = left upper lobe, V = left lower lobe.

The relations between membranes and breathing and the respiratory difficulties in premature infants during the first days of life are illustrated by the circumstance, that out of the 27 premature live-born infants of my material, who died on the first day of life, only 9 were such who did not show any formations that could be interpreted as membranes. I have considered as affected with membranes all such cases, where formations of this character could be found even in one lobe, therefore there are such cases in this group who had a very small amount of membranes.

Membranes as a Cause of Death

On tables 19, 20 I present the death causes of subjects affected with membranes according to the probability which could be inferred on the basis of post mortem and clinical findings. As illustrated by the table, I have regarded membranes as a cause of death of fullterm babies only in two cases. In the third case (N 589/ II/46) the evident cause of death was jointly fetal asphyxia, aspirat-

ion of the amniotic fluid and membranes. As far as all the other fullterm infants are concerned, I feel the membranes cannot be regarded as more than partly responsible for death, or as secondary findings.

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With regard to the prematures, I have considered the part played by membranes so great in seven cases, that they can be held responsible for the death at least as a contributory factor of great significance, or taken as the only cause of death. When estimating the cases, I have paid attention to the clinical history, the post mortem findings and the amount of membranes. Even in such cases, where membranes were the only objective finding and the cause of death was clinically unclear, I have not regarded membranes as a cause of death, if they were scarse. In this group there are also cases where the cause of death is evidently another than the membranes, and these are only secondary findings. It is naturally difficult to estimate in every individual case what is the share of the membranes as cause of death, but it is still possible to say that they are secondary findings at least in some cases.

Conclusions. — Membranes originate from the aspirated amniotic fluid, but in all probability, the proper pulmonary cells which come off also have a part in the formation of membrane substances in the prematures and above all in the immatures. In my material membranes are more often found in the prematures than in the fullterms, and possibly more often in the immatures than in the prematures. Often an extra-pulmonary cause of quickened breathing is revealed, but there are also cases, where membranes as such must be regarded as the reason of respiratory disturbances, both clinically and on the basis of post mortem findings. It can be supposed that in such cases the formation of membranes began as a result of difficult labour and aspiration of the amniotic fluid.

Membranes can be regarded as a cause of death only in part of the cases. In addition, they were a contributory factor to the cause of death of some cases. In part of the cases they must be regarded as secondary findings. Approximately in half of the cases affected with membranes these must be considered the principal cause of death, or at least, an important contributory factor.

Thus, the presence of membranes as such is not sufficient to prove that they have caused death, but their amount as well as other post mortem findings and the clinical history must also be taken into consideration. It seems indisputable that membranes can come off and disappear, and therefore they need not necessarily be fatal.

It is probable that membranes for their part can also be a reason of respiratory disorders, and in some cases — the sole reason. Sometimes a *circulus vitiosus* can come into existence, where on the one hand membranes are born as a consequence of respiratory disturbances, but on the other — respiratory disturbances are caused by them, in consequence of which more membranes appear, or the membranes thicken.

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Fetal State of the Lungs. Intra-Uterine Breathing. Congenital Atelectasis. - As already said, it is impossible to draw any certain conclusions on the basis of post mortem material as to the extension of the lumina in the course of an undisturbed intrauterine life. The process of labour and the exposure to air are factors which must be thought to exercise a great influence on the condition of the fetus. and changes can always take place in the placental circulation that activate the fetus into breathing. Already in a 23 cm. long fetus thoracic movements can be noted when the fetus is removed from the uterus (Minkowski), this can even be the case in a 85 mm long fetus (WINDLE et al.). It is therefore clear that even when examining quite small fetuses, the lumina microscopically revealed in the lungs can have appeared under the influence of the respiratory movements the fetus made when dying. This must also be taken into consideration when estimating the results of Bender's researches, although he began his examinations on fetuses only 9 weeks old. It is therefore impossible, on the basis of anatomic findings. to furnish any conclusive proof of the presence of lumina in the lungs in the fetal state. Since a determination of intrauterine breathing by means of histologic sections is based on the findings of extended lumina, it must be admitted that it is hardly possible to ascertain any intra-uterine respiratory activity on the basis of antomic observations. It is equally difficult to settle the question of a physiological aspiration of amniotic fluid in the fetal state, which is closely connected with the size of the lumina and intrauterine breathing, in the light of anatomic observations. According to my material it is possible to say that evidently newborn infants have liquor amnii substances in their lungs. This does not prove that it was so in the fetal state.

X-ray examinations of human fetuses do not yield any conclusive evidence with regard to intra-uterine breathing and aspiration of the amniotic fluid, as the possibility is also present here that the fetus had aspirated in consequence of the manipulations. Yet the positive results obtained with them have in my opinion a greater power of evidence than anatomic observations, and if their results are compared with those of animal tests, it appears highly probable that the human fetus aspirates amniotic fluid in utero. The occurrence of intra-uterine respiratory movements must now be regarded as proved on the basis of researches made already by Ahlfeld, and of late by Snyder and Rosenfeld as well as Bonar.

In my own material, the lumina always found in the fetal lungs and the amniotic fluid substances present in the lungs of nearly all newborn infants, also speak in my opinion on behalf of intra-uterine breathing, even if I cannot consider them as any conclusive evidence. If it is now admitted that the fetus breathes in utero and physiologically aspirates amniotic fluid, it is hardly logical to suppose that this latter will stop in the trachea. Moreover, the roentgenography contrast medium did reach the lungs in the experiments made with human fetuses (see p. 20 in the survey of literature). Even if it must be taken into consideration, that this aspiration may be artificially induced, it must be admitted on the other hand, that corresponding stimuli can have their effect on the fetus also in an undisturbed intra-uterine existence, due to contractions of the uterus (SZENDI). If the fetus aspirates amniotic fluid down to the pulmonary tissue, it follows that lumina must be found also in the pulmonary tissue, nor are the walls in close contact to each other in the fetal state. In my material unmistakable lumina were to be found everywhere in the pulmonary tissue, both in the lungs of kittens killed in utero, and in the human fetuses who had died during pregnancy or in the birth process. The sizes of the lumina were similar in the lungs of the cat fetuses killed in the same manner, but in the fetus that was suffocated intra-uterinally by aspirating amniotic fluid, the lumen was clearly larger. There were considerable variations in the lumen size in the lungs of fullterm human fetuses. This was evidently dependent upon how much the fetus had aspirated during pregnancy or labour. The variations were great also in such cases where a compression of the umbilical cord was ascertained. The size of the lumina is not probably solely determined by the potency of the factors provoking respiratory movements during labour or pregnancy, but also by other factors as well — during labour e.g. by the quantity the fetus is able to aspirate. It is of course natural, that a fetus whose mouth — during the compression of the umbilical cord — is strongly pressed against the walls of the genital passages, or if his thorax is compressed by them — cannot aspirate to the same extent as a fetus who has his mouth and thorax free. In all probability the extension of the lumina is determined by other factors also, because this is not sufficient in itself to explain the variations of the lumen size in my material.

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It is not possible to determine with the help of my material, to what an extent the lumen sizes vary physiologically. If the fetus respirates amniotic fluid in utero in and out, this also presupposes variations in the sizes of the lumina. I feel that we must regard as *normal size* of the fetal lumen the smallest size which can be found in the post mortem material. The lumen ratio in the histologic section of the lungs of a fullterm fetus is then 15 % of the whole area counted in one dimension. The lumina of premature fetuses are, according to my material considerably smaller. They vary in fetuses of a different weight, having a minimum of 5 %. They are also visible in this case, but are so small that the walls touch one another in places.

The fulltime fetuses of my material have considerable variations in the sizes of their lumina. As a rule, the lumina of specimens taken from different lobes of the same lungs are about the same size. According to animal experiments, the dilatation of the lumina in the lungs of the cat fetus killed in utero is more or less uniform in the different parts. With the dilatation of the lumina, the pulmonary structure remains otherwise unchanged. As already said, considerable changes were revealed in different cases also in the lungs of the human fetus. Yet their other characteristics were similar. There were intermediate forms between the highest and lowest lumen ratio. It would therefore be an artificial idea if a certain lumen size did not belong to congenital atelectasis. Nor does it appear reasonable to describe as congenital atelectasis only such

cases which do not have any lumen - irrespective of the point of view one adopts in regard to the lumen size in the fetal state. In that case the result would be that the lungs of a stillborn fetus would exceedingly seldom - if ever - be congenitally atelectatic, even if it had not inspirated any air. The simplest course to adopt in determining congenital atelectasis is to revert to Jörg's original determination. According to it, lungs are (congenitally) atelectatic as long as they have not yet expanded under the influence of air. Therefore the size of the lumen in congenitally atelectatic lungs can vary in different cases. Congenital atelectasis is then not identical with the fetal state of the lung, but I feel that this determination is better adaptable in practice and seems to correspond better to our conception of the nature of congenital atelectasis than in case the size of the lumina is used as a standard for determination. In addition, there is the advantage that this determination does not, when speaking of congenital atelectasis, demand any definite attitude with regard to the fetal state of the lung -- above all, the size of the lumina ante partum.

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Aspiration of the amniotic fluid should according to the above, be assessed in conformity to the extension of the lumina. However, this can only be said provided the lumen does not have any other contents than amniotic fluid. Yet this circumstance is not selfevident. The animal tests revealed that the lumina of the cat fetus regularly had cells which looked like epithelial cells, with a great number of vacuoles. Corresponding cells were found in the lungs of the human fetus. In addition there was, especially in the latter, a regular and constant finding of a precipitated substance which was often the principal contents of the lumen. This substance is probably, at least to the greatest extent, amniotic fluid, but it could not be proved as such on the basis of its morphologic and tinctorial characteristics. If it is not regarded as amniotic fluid it must be surmised that it has been aspirated from the genital passages or is a product of the lungs themselves. It may be a result of glandular secretion or a residue born in the process of the evolution and growth of the lungs. The circumstance that epithelial cells that have evidently come off the walls are found in the lumen, speaks on behalf of the theory that their disintegration can be partly responsible for the formation of this substance. It was some-

times possible to demonstrate in this mass that a very small part of it stained red with mucicarmine, whereas there was simultaneously in the bronchial glands a considerable quantity of substances, staining in the same way. This supports the surmise that part of the substance can be mucus, born as a result of the secretion of the bronchial glands. If the substance has originated in the lungs, it means that its disappearance necessitates a flow from the lungs in the direction of the trachea. This flow need not be a consequence of inta-uterine respiratory movements, as it can be surmised that the cilial motion alone would be sufficient to remove the substance. Cases in which a congenital larvnx atresia was found, and simultaneously widely expanded lumina in congenitially atelectatic lungs. filled with mucus (Frankenberg, Kovacs) bear out the theory that there is normally a flow of substances from the lungs into the amniotic fluid. The presence of epithelial cells and squamae from the skin is a much surer sign of aspiration of liquor amnii than this precipitated substance and it is easier to determine their quantity. Even if these quantities vary in the amniotic fluid, presenting in individual cases different pictures of the extent of the aspiration, I consider their determination to be the surest method of assessing the extent of the aspiration. There are difficulties in estimating the quantity of »physiologic» aspiration; this type of aspiration is best represented in a case, where the process of labour has as little influence as possible on the fetus. In the fullterm fetus who had the smallest lumina in the material, the aspirated quantity was rather abundant and appeared in all the lobes. If the smallest determined quantity is taken as a standard for physiologic aspiration, particles of the amniotic fluid are found in every lobe, although their quantity is insignificant. In that case the quantity of cells and squamae is so small that the amniotic fluid filling the mouth of the fetus, can be surmised to be sufficient for it. In my material the aspiration is generally smaller in premature than in fullterm infants, in accordance with the smaller size of their lumina. - It is possible that the extent of the physiological aspiration also varies. It is also possible, within certain limits, to estimate the extent of intra-uterine asphyxia on the basis of the expansion of the lumina in congenitially atelectatic lungs, but in cases where air has already entered the lungs, this is no longer possible. The amount of aspira-

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ted substances can then give an idea of the extent of aspiration. There are cases in my material revealing evident intra-uterine asphyxia and a small quantity of aspirated substances, and on the other hand, cases with no signs of intra-uterine asphyxia and abundant amounts of aspirated substances. In order to be able to understand these cases we should, I feel, support to a certain extent the explanation given by Schultze, according to which transient intrauteripe asphyxia can be the cause of aspiration and, on the other hand, a slowly and gradually appearing oxygen want which does not cause aspiration. Thus, it is not always possible, on the basis of the amounts of aspirated liquor amnii substances, to draw definite conclusions as to whether the infant was born asphyxiated or not. However, it seems that such exceptions are rare. The impression is gained from my material, that as a general rule, strong aspiration is a mark of intra-uterine asphyxia - especially such as has occured during labour or its final stages but that, even if the fetus was clearly asphyxiated, abundant amounts of aspirated amniotic fluid are not always found in the lungs. It is of course evident that the amount of aspiration is influenced partly by the same factors as the extension of the lumina (see above). It is therefore difficult to determine when the aspiration must be regarded as pathological, in the sense that it is an indicator of fetal asphyxia. Thus, my material seems to demonstrate that there can be a moderate or even insignificant aspiration, though the fetus was asphyxiated. The »physiological» aspiration is quite small. The division between these conditions is difficult to draw, still less can any figures be stated according to which it would be possible to determine the amount of aspiration as an indicator of asphyxia. Yet it is possible to say that, without any special causative factors, aspirated substances are found in all the lobes of the lungs of infants born at term. The amounts are often smaller in prematures, and substances may be found only in some parts of the pulmonary lobes.

Aeration of the Lungs and Pulmonary Factors Influencing it. — Post mortem material has its limitations with regard to the estimation of aeration. The collapse of the lungs which sets in postmortally can greatly change the intra vitam aspect. As already mentioned it is, notwithstanding, possible to draw conclusions

on the basis of my material, the methods of procedure having been identical in all cases. In my animal experiments I have endeavoured to restrict the postmortal changes to the minimum, hecause in them a comparative quantitative estimation was made of the aeration in different cases. In my post mortem material I have drawn no conclusions on the basis of measuring the extent of the lumina. My sole endeavour was to determine by examining the section, whether some area had ever been air-containing. In this respect an aerated area and one affected with secondary at electasis are equivalent. In microscopic sections, it may be a matter of interpretation as to when some area is to be considered as having become atelectatic. It was demonstrable in the animal tests that unmistakable lumina could be seen microscopically even in such lungs of kittens, which macroscopically appeared completely airless and did not float, only part of these lungs being completely deficient in lumina. The post mortem material shows intermediate forms, from widely extended lumina to a nearly complete deficiency in them. In determinations of atelectasis a completely airless condition is often mentioned (see p. 14), but in addition, also a decrease of aeration (Bergstrand). For secondary atelectasis mention is made of the possibility of contents in lumina (Hanson and SJÖSTRAND), these contents having the appearance of edema fluid. In atelectasis caused by compression I have found in macroscopically completely airless lungs of infant 4 months old, that a microscopic examination revealed clear though excedingly small slitlike lumina. -- If the concept secondary atelectasis is to be confined within the same limits as congenital atelectasis, airlessness must be regarded as one of its characteristics. This, as explained above, does not mean the same thing as a complete absence of lumina. Microscopic sections can reveal empty lumina, if the contents are such that they do not fix. But some empty or nearly empty lumina can also be seen in congenital atelectasis, though it is evident that no air has entered the lungs. There are borderline cases in both groups, where it is difficult or even impossible to estimate whether a certain lumen is atelectatic or air-containing.

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As already mentioned, the determination of the concept secondary atelectasis has no significance for the results of my researches. Atelectatic areas were demonstrable in all the cases examined by me. Even if possible postmortal changes are disregarded, small atelectatic areas cannot be considered as evidence of a pathologic state, as it is most probable that there are also some physiologically airless collapsed areas in the lungs, — as it was proved by Verzar's and Jeker's animal experiments.

A determination of the aeration of the lungs in accordance with the disappearance of congenital atelectasis harbours, in addition to the difficulties of interpreting the sections, also some possibilities of errors. Theoretically it is possible that some area can collapse and take on the aspect of secondary atelectasis without having become aerated in between. My animal experiments argue against this possibility, but as they could be made use of only if carried out with kittens a few hours old, they do not eliminate the possibility of such a state of things in subjects with a longer term of life. On the other hand, the structure of lungs affected with secondary atelectasis can alter so that the epithelium becomes regularly isoprismatic, which makes it difficult to differentiate them from congenitally atelectatic lumina. This can happen, according to Mov-LONGUET'S test, in dogs already within 6 days. It is difficult to determine with what rapidity such changes take place in the newborn. In my opinion, this should be taken into consideration when determining, on the basis of morphologic characteristics, the extent of respiratory activity in the lungs of infants several weeks old. It is possible that this circumstance is responsible for the erroneus conclusions published in literature with regard to the persistence of congenital atelectasis.

It seems that animal experiments do not justify conclusions as to how rapidly the aeration progresses in man. Although there is no considerable difference in the structure of lungs of kittens and newborn infants, that of the former being however somewhat more simple, there is such a great difference in the vitality, that there are reasons to surmise a quicker aeration in kittens than in newborn infants. This being so, the circumstance that the lungs of kittens were already fully air-containing one hour after birth does not by any means justify the contention that this is the case in human lungs. On the other hand, it must be taken into consideration that when examining the lungs of infants who had died in hospital, it is not possible as a rule to obtain for examination

a baby a few hours old, who had been brisk and breathed well the whole time.

I have endeavoured in my experiments to make clear how quickly the lungs can become aerated. If the question is posed thus, different results are arrived at than when attempting to determine, how long congenital atelectasis can persist. It is therefore evident that my material vields different results than the researches of FARBER and Wilson, based on an extensive material. The impression is gained from my material that a few inspirations suffice to bring about an expansion including the outermost periphery in lungs of fullterm infants, although this is not demonstrable by post mortem examinations in all parts of the lungs, some parts remaining atelectatic. Therefore it is not possible to deny, on the basis of post mortem material, that the lungs of a brisk infant breathing well may become fully aerated in the course of the first few hours. This evidence was not to be found in my own material, the aeration having been slow in my cases. Still, it can be maintained on the basis of my material that the expansion is not a matter of weeks, but days - not excluding premature or even immature infants. According to this, the aeration is somewhat more rapid in fullterm than in premature infants, and I have come to the conclusion, in the light of my material, that the expansion of the fullterm lung takes two-three days, which conforms to the results of FARBER'S researches. The lungs can also become areated in prematures already after a few indrawn breaths, but this was only demonstrable in limited areas comprising at the utmost the areas of one lobe — i.e., clearly less than in fullterm babies. A breathing of five days duration has been sufficient for an aeration of all parts of the lungs of a premature infant under 1000 g. of weight. I do not wich to deny the possibility that congenitally atelectatic areas can persist for weeks in a premature lung (FARBER and WILSON), but I feel it can be assumed in that case that there might have been factors exercising a restraining influence on the aeration, which cannot be detected anymore in a post mortem examination.

Therefore, although it is sometimes possible to observe an aeration including even the most peripheric parts, post mortem findings in the lungs of both fullterm and premature babies succumbed in the course of the first few days of life show the aeration to have

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been such, that the outermost periphery has retained its small lumina, whereas the central parts of the alveolor tree became fully air-containing. This state can be met with also in cases which have become secondarily atelectatic. It is therefore conceivable that this has appeared postmortally, after the collapse of the lungs. Such a possibility cannot be completely disregarded, but the circumstance that vernix membranes were as a rule found solely in these expanded places, strongly argues in favour of the surmise that these formations appear intra vitam. Nobody ever reported having found vernix membranes in babies who had not breathed air, and in my own material membranes were only met with in aerated lungs.

The different rapidity of aeration in different pulmonary areas can be related to the various stages of their development. This is borne out to some degree by the different state of development of the elastic tissue in distinct parts of the lung. (See Setälä).

Since post mortem examinations invariably demonstrate amniotic fluid substances in lungs of babies under three days old, and since it appears probable that all newborn infants have liquor amnii in their respiratory passages, this factor must be taken into consideration as possibly exercising an influence on the aeration of the lungs. »Physiological» aspiration does not seem to have any special significance in this respect. The circumstance that the expansion is slower in the periphery than in the central parts can be due to some extent to the aspiration of amniotic fluid. It is often visible in the sections how the peripheric narrow lumina are filled with substances, that are partly unmistakably, partly probably, liquor amnii substances. It is therefore conceivable that, with the rush of air into the lumina, the amniotic fluid in them withdraws towards the periphery and disappears gradually, partly under the influence of respiratory movements and partly through absorption. Then only do the peripheric parts also become aerated. It is evident that air can penetrate also down to the periphery and the amniotic fluid substances become plastered against the walls of the extended lumina. Depending on the amounts of amniotic fluid and the character of the respiratory activity - perhaps also on the nature of the amniotic fluid - its substances remain in the walls for a short time and disappear already with the following breaths, or the substances adhere to the wall and form vernix membranes. If the aspiration is abundant, it can result in suffocation without any formations of membranes. Some areas can be so full of amniotic fluid substances, that air cannot peretrate them at all. However, the lungs become partly aircontaining in such cases, even if there are abundant amounts of liquor amnii in the trachea, and I feel that we can speak of suffocation by amniotic fluid only provided agration can be ascertained. An intra-uterine suffocation by amniotic fluid is only the result of completely illogical thinking.

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With the gradual withdrawal of the liquor amnii substances from the lungs, it is conceivable that after the cleansing of the pharynx and larynx, these substances can again be found in the upper respiratory passages. This is not therefore necessarily a formation of mucus due to irritation of the respiratory passages. It cannot be denied of course that mucus can be secreted in consequence of an irritation by foreign substances. In my material, mucus could be demonstrated tinctorially in small quantities in the deeper parts, but there was often more of it in the bronchial glands and mucous membrane — yet never in any significant quantities. Thus, in the light of this research, the substances found in the neonatal lung are mainly liquor amnii substances — also however containing such, whose origin it is difficult to determine.

Elements from which membranes result are mainly amniotic fluid, at least in fullterm infants. To produce these membranes, aspiration exceeding the quantity of »physiological» aspiration is necessary. Intra-uterine asphyxia is not a constant finding, by which the abundant aspiration could be explained. It can be surmised that it is a result of earlier transient intra-uterine asphyxia, or it can have occurred at the final stages of labour, so late that there was no time for the symptoms of asphyxia to appear during the process of labour. My material does not contain cases which could lead me to suppose, that the amniotic fluid substances concentrate in the walls of the lumina already during intra-uterine existence (comp. Erhardt's x-ray researches, p. 24). According to my material, the membranes in prematures often contained cells detached from the walls of lumina, which had undergone changes --- disintegrated into a partly structureless substance before they had formed membranes. A similar mass can sometimes also be formed by amniotic fluid substances. It is therefore conceivable that such masses had originated solely from amniotic fluid substances. I feel however that I have been able to ascertain intermediate forms, from detached cells to complete membranes. I therefore consider that my material makes it evident that cells detached from the walls also play their part in the formation of membranes in premature infants. For fullterm babies, I have been unable to conclusively ascertain such forms, but in one case there were observations pointing in this direction. Therefore, I do not consider that the formation of membranes in fullterm and premature infants is necessarily different. In prematures membranes also clearly result from amniotic fluid substances. There is every reason to maintain the name vernix membrane, since the part played by the amniotic fluid in the formation of membranes is most evident and conclusive. The formation of membranes does not presuppose any inflammatory processes, as membranes were often present in lungs without any signs of inflammation. In connection with another research of mine I have found that membranes do not occur more frequently in pneumonic than in noninflammed lungs. Taking into consideration the high incidence of membranes in my material, it is evident that they also have a clinical significance. They can appear in such small amounts that they do not seem to involve any particular respiratory disturbances, but in some cases they are present in such abundant quantities, that they are the only cause of death according to the post mortem examination. My material makes it evident that membranes appear simultaneously with the first indrawings of breath. Therefore their occurence should be taken into consideration when looking for the cause of difficult respiration on the first day of life. Still, membrane formations can be the cause of respiratory disturbances continuing for several days. In such cases it could not be proved that membranes had originated from the amniotic fluid substances. It is possible that membranes can appear in the newborn without any relation to aspirated liquor amnii. It is however certain that the main part of membranes in the newborn are formed from the amniotic fluid substances, and if there are membranes resulted in a different way, they are a most uncommon occurrence.

There is not a single membrane case in my material with necroses in the walls. The walls covered with membranes have not shown any different structure than the areas free from membranes.

In the light of microscopic sections, it appears that membranes prevent the aeration of the lungs. When a comparison was made between the groups of cases affected with membranes and free from them, the difference was not clearly visible. Examinations of twins and especially triplets provide a strong argument in favour of the surmise that the amounts of membranes are significant, both with regard to the duration of life and to the aeration of the lungs. Considering the position of the membranes, it is quite natural that they are a most significant factor, especially in prematures, impeding the exchange of gases. They occur most frequently in fact just in those parts where the greatest quantity of capillaries contact the lumina and which have become air-containing. In this way the membranes injure the oxygen supply, difficult of itself in premature infants. According to my material, vernix membranes are the most important (non-inflammatory) pernicious result of the aspiration of amniotic fluid.

Summary

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Definite conclusions about intra-uterine breathing and the fetal state of the lung cannot be drawn solely on the basis of post mortem material and histologic examinations of lungs of animal fetuses — especially with regard to whether there are lumina in the lungs and how much they are extended already during intra-uterine existence. Lumina in the fetal lung were found in every instance but no evidence can be produced that a corresponding state prevails in an undisturbed intrauterine existence. The lumina expand during fetal aspiration of the amniotic fluid, if the placental circulation is disturbed or interrupted. This was fully demonstrable in the animal experiments, and the post mortem material argues in favour of the surmise that this also is the state of things in the human fetus. Thus, the extension of the lumina in the fetal lung is some kind of a standard for measuring the extent of intra-uterine asphyxia.

In determining congenital atelectasis, it is best to revert to Jörg's original determination, according to which the lungs are congenitally atelectatic as long as they are not expanded through the influence of aeration. Post mortem examinations of congenitally atelectatic lungs always reveal lumina, and their sizes vary considerably, although the structure of the lungs remains otherwise unchanged. The lumen size is approximately the same in different places of the same lung. The smallest lumina were found in premature fetuses.

In the light of post mortem material, amniotic fluid is always to be found in the neonatal lung, which enables us to speak of a »physiologic» aspiration of the amniotic fluid. The amounts however usually appear small. The extent of the aspiration can vary in individual cases, without any reason being demonstrable for a stronger aspiration than usual. Small amounts of aspirated amniotic fluid have no noxious effect on the newborn. A strong aspiration can result in suffocation, in which

case the lungs become partly air-containing. Fullterm infants aspirate more than prematures, although abundant aspiration can sometimes also be found in the lungs of the latter. Vernix membranes are a comparatively frequent finding in the neonatal lung; they are formed mainly from amniotic fluid substances, but at least in premature infants, they can partly result from disintegrated cells which have become detacked from the walls. These membranes are found only in aerated lungs, though they can be present in the lungs of babies who had died during labour. They must be taken into consideration as a cause of neonatal death, and are only revealed by a microscopic examination.

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In the light of the material on which post mortem examination on be made, the process of aeration is gradual in both fullterm and premature infants. It is more rapid in the fullterm than in the premature, but the material does not disclose any considerable difference, since the process of aeration lasted for 2-3 days in the fullterm, and was complete in the premature lungs already of the 5th day of life. It seems however that a few breaths are sufficient to result in an almost maximum aeration of the fullterm lungs. The possibility cannot therefore be denied that the lungs of a fullterm infant with good breathing may become fully air-containing already in the course of the first day of life. This is much less probable with regard to the prematures. According to the post mortem material, the expansion of the lungs with air occurs in such a way, that the central parts of the alveolar tree are the first to expand, after which the outermost periphery gradually becomes aircontaining. As an exception, the expansion can take place in some lungs in the whole area of the alveolar tree. The manner of expansion is the same both in premature and fullterm infants, although it is better visible in prematures, especially in the smallest babies, since the periphery becomes areated more slowly than in the fullterms.

The expansion can be delayed by aspirated amniotic fluid and vernix membranes.

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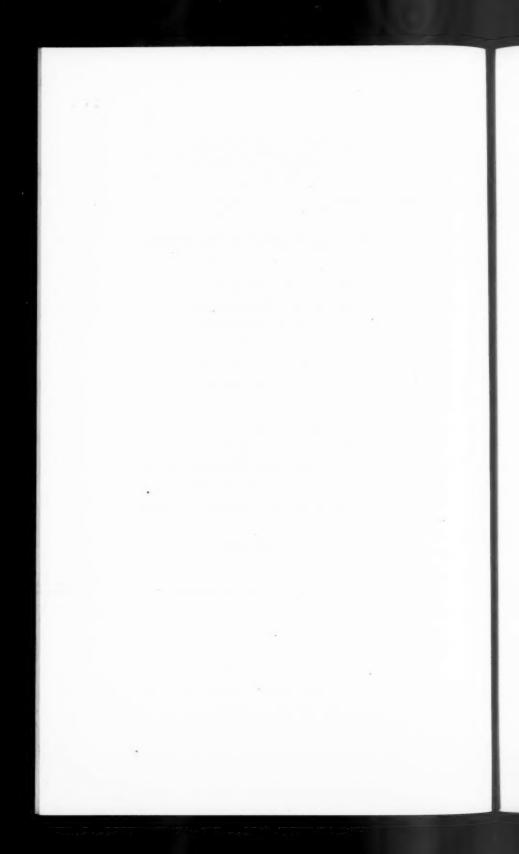
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ILLUSTRATIONS

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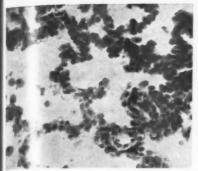


Fig. 1 Congenitally atelectatic lung of cat, with a tuous, mina almost empty. (Cat 11/I, upper part of right lung. Hematoxylin and van Gieson. × abt 200.)

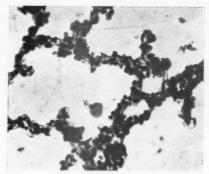


Fig. 2. Lung of cat suffocated in utero, with a lumen ratio of abt. 60 %. Walls are straighter than in preceding case. Small amounts of contents in lumina. (Cat 10/II. Hematoxylin and van Gieson. × abt 200.)

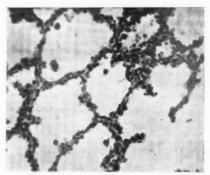


Fig. 3. Lung of cat which inhaled some air. No essential difference as compared to fig. 1 and 2. (Cat. 7/III. Hematoxylin and cosin. × abt 200.)

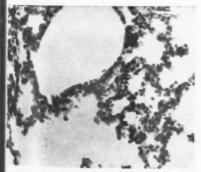


Fig. 4. Lung of cat which survived for an hour. The figure clearly illustrates the tension of the wall in an aerated area. (Cat. 6/I. Hematoxylin and van Gieson. \times abt 200.)

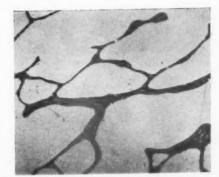


Fig. 5. Lung of cat which survived for 42 hours. All lumina visible in the fig. are aircontaining and the pulmonary structure clearly differs from that of a lung with congenital atelectasis. (Cat 8/II. Hematoxylin and mucicarmine. × abt 100.)

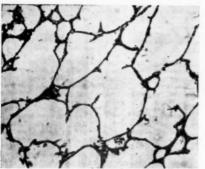


Fig. 6. Lung of cat surviving for 45 minutes, which is fully aerated. Walls are thin and *tense*. (Cat 11/II. Hematoxylin and eosin. × abt 50.)

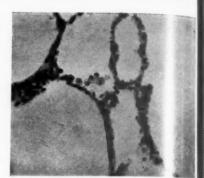


Fig. 7. Same as in fig. 6. \times abt

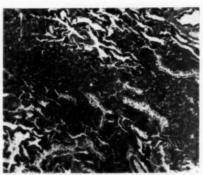


Fig. 8. Lung of cat with secondary atelectasis. Lumina are to be found only in the peripheral parts of the fig. The tissue in the central parts is deficient in lumina. (Cat 7/II. Hematoxylin and van Gieson. × abt 50.)

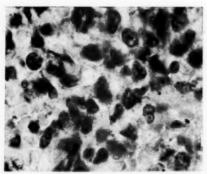


Fig. 9. Lung of cat with secondary atelectasis. The tissue has no lumina. (Cat 1/V. Hematoxylin and van Gieson. × abt 900.)

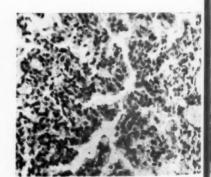


Fig. 10. Lung of cat with secondary atelectasis. Narrow lumina. (Cat 1/V. Hematoxylin and mucicarmine. × abt 200.)

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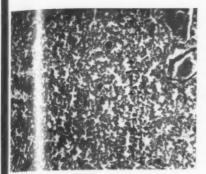


Fig. 1. Lung of fetus with congenital atelectasis. The fetus was born asphyxiated and did not restricted. Small lumina, tortuous walls. (Case 1979/1/46. Birth weight 2980 gm. Ht.natoxylin and eosin. X abt 50.)

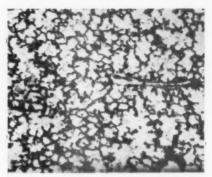


Fig. 12. Lung of fetus with congenital atelectasis, with unmistakably larger lumina than in fig. 11. Abundant contents in the lumina. Fetus died in the course of delivery. (Case N 810/H/45. Birth weight 3300 gm. Masson's staining. \times abt 50.)

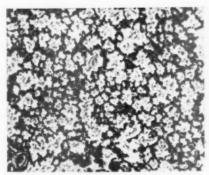


Fig. 13. Lung of fetus with congenital atelectasis, where the lumina are of abt. the same size as in fig. 12. The lumen ratio was clearly different in these cases. (Table no. 5). This difference is due to the different thickness of the walls. (Case N 2686/H/45. Birth weight $3000~\rm{gm}$. Haematoxylin and eosin. \times abt 50.)

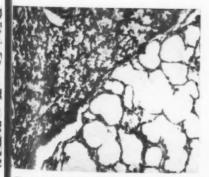


Fig. 14. Partly congenitally atelectatic, partly agrated lung. The borderline between these areas is pronounced. Fullterm fetus who died during labour. (Case K 719/45. Birth weight 375 gm. Masson's staining. × abt 50.)

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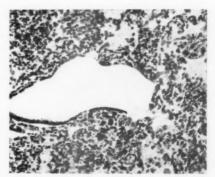


Fig. 15. Partly aerated lung of infant who survived for 24 hours. The outermost periphery is not aerated. Abundant amounts of vernix membranes. (Case N 494/II/45. Birth weight 2870 gm. Hematoxylin and eosin. \times abt 100.)

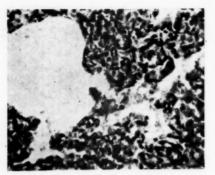


Fig. 16. Same case as Fig. 15. This case had abundant membranes. The fig. does not illustrate areas affected with membranes. It is clearly visible that the outermost periphery is not aerated. × abt 300.



Fig. 17. Pulmonary tissue which ha partly air-containing. Fullterm fetuborn asphyxiated, not resuscitated 979/I/46. Birth weight 2980 gm. Hen and van Gieson. × abt 100



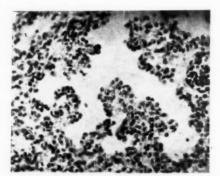


Fig. 18. Pulmonary tissue of immature fet us, with unmistakable lumina, but construction of the walls similar to that of non-aerated lungs. (Case K 425/45 B. Birth weight 670 gm. Hematoxylin and van Gieson. \times abt 200.)

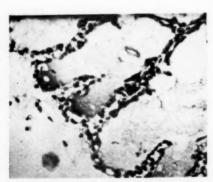


Fig. 19. Extended lumina in the areas below the pleura in the lungs of an immature fetus. It died in the course of the delivery. (Case N 352/II/45. Birth weight 1040 gm. Hematoxylin and eosin. × abt 200.)

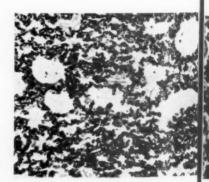


Fig. 20. Partly aerated lung of premature infant who died during delivery. Air-containing lumina have *tense walls*. Medium amounts of aspirated substances in the lungs (Case N 1521/II/45. Birth weight 2000 gm. Hemato-xylin and eosin. × abt 100.)

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Fig. 21 Lungs of immature infant affected with secondary atelectasis. It survived for five days. (Case P 203/45. Birth weight 970 gm. Hematoxylin and eosin. × abt 50.)

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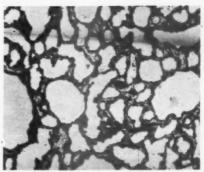


Fig. 22. Fully expanded lung of immature baby. It survived for one hour and a half. (Case K 720/45. Birth weight 920 gm. Masson's staining. × abt 50.)

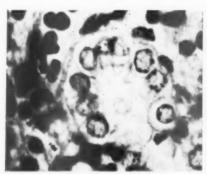


Fig. 23. Pneumonomeres of premature infant. The structure is regular, the cells have a somewhat similar form and their arrangement is regular. Capillaries are searse. Lumina are small, but clearly visible. The baby survived for 13 minutes. (Case N 788/I/45. Birth weight 1360 gm. Hematoxylin and eosin. \times abt 900.)

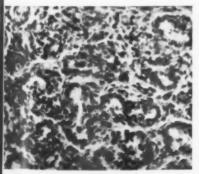


Fig. 24. Lung of premature who survived for half an hour. The fig. does not show aircontaining lumina. — The structure is regular. Abundant amounts of loose tissue between the pneumonomeres. (Case K 2621/45. Birth weight 2080 gm. Hematoxylin and eosin, × abt 200.)

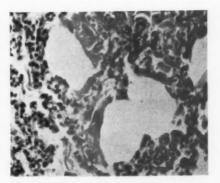


Fig. 25. Liquor amnii squamae are close to the walls in air-containing lumina. Lung of fullterm fetus who died during delivery.(Case K 643/46. Birth weight 3740 gm. Hematoxylin and eosin. × abt 200.)

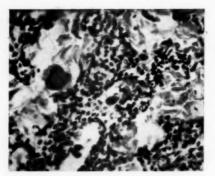


Fig. 26. Abundant aspiration of amniotic fluid in lungs of immature baby. It survived for two hours. (Case N 852/I/45. Birth weight 980 gm. Masson's staining. × abt 200.)



Fig. 27. Drops of fat in bronchial eg Premature infant, survived for fo (Case 531/II/46. Birth weight 1560 g and hematoxylin. × abt 40



Birth

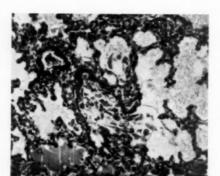


Fig. 28. Abundant quantity of amniotic fluid substances in *bronchioli*. More to the periphery only precipitate in the lumina (same case as fig. 19. × abt 100.)

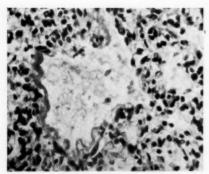


Fig. 29. Vernix membranes in lumina which contain precipitate. The membrane substances are not discernible in the figure. (Case N 494/II/45. Birth weight 2870 gm. Hematoxylin and eosin. × abt 200.)

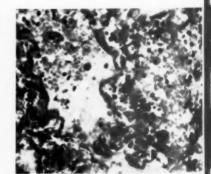


Fig. 30. Membranes in lungs whose lumina contain considerable amounts of blood. Fulterm infant who lived for 13 days. (Case P 276/46. Hematoxylin and eosin. × abt 200.)

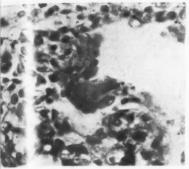


Fig. 31. nmistakably air-containing lumina filled with a mass showing dark particles. This masseems partly to be formed by cells coming of the walls. (Case N 2663/I/45 B. Birth wight 1470 gm. Hematoxylin and eosin. \times abt 400.)

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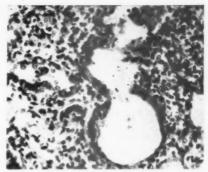


Fig. 32. Membranes in lung of immature baby. Membranes covering lumina withstense walls. (Case L. 94/46. Birth weight 920 gm. Hematoxylin and eosin. × abt 200.)

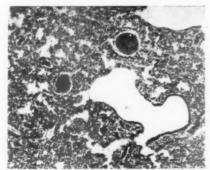


Fig. 33, Fig. 34, Fig. 35. Different degrees of expansion in the lungs of triplets N 519/II/46 A, B and C. The largest dilatation is unmistatably that of fig. 35 (Baby C). In fig. 33 (Baby A) and 34 (Baby I) the dilatation is about similar. The membranes of these cases are not visible in the figures. (Hematoxylin and cosin. × abt 50.)



Fig. 34:

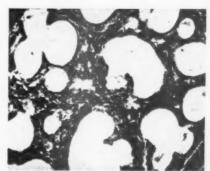


Fig. 35.

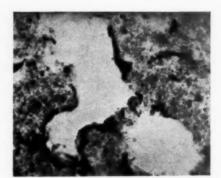


Fig. 36. Vernix membranes in the lungs of an infant who survived for four hours. (Case N 575/II/45. Birth weight 1070 gm. Sudan and hematoxylin. × abt 200.)

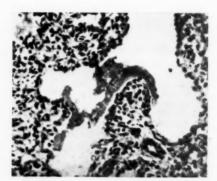


Fig. 37. Vernix membrane. Structure not discernible everywhere in the membrane, and it is of an almost homogeneous substance. (Case N 930/I/45 B. Birth weight 2220 gm. Hematoxylin and eosin. × abt 200.)





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EDITOR PROFESSOR A. LICHTENSTEN

KRONPRINSESSAN LOVISAS BARNSJUKHUS,
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ACTA PÆDIATRICA





ON THE CHANGES IN THE PERIPHERAL BLOOD PICTURE OF THE NEWBORN INFANT IMMEDIATELY AFTER BIRTH

BY

RUTH WEGELIUS

ACTA PAEDIATRICA, VOL. XXXV. SUPPLEMENTUM IV

HELSINGFORS 1948

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PREFACE

To begin with I would like to express my most humble gratitude to my teacher and chief, Professor Arvo YLPPÖ who has always shown great interest in my work and encouraged me. The assistant Chief Physician of the Children's Clinic, C. E. RÄIHÄ, M. D., suggested the idea of this investigation and, in the course of its progress has given me his advice and opinion both of which have been of great value to me. I also want to thank the leaders of the University's I and II Gynecology and Obstetric Clinics, Professor Mauno Rauramo and Professor AARNO TURUNEN as well as the Chief Physician of the Midwifery Institute in Helsingfors, Professor Aulis Apajalahti for kindly giving me permission to examine babies in their departments, and for allowing me to work in their laboratories. I especially want to thank the staff of these departments for all the kindness shown. The assistant of the Astronomical Observatory, University of Helsingfors, BERTIL OVIST, M. A., has assisted me on the statistical side and with interpretion of the material, and I herewith want to thank him for his great help.

I have been granted economic support by the »Svenska Kulturfonden» (Swedish Cultural Relief Fund, Helsingfors) and »Finska
Läkaresällskapet» (The Finnish Medical Society). I have also had
help from The General Officer Commanding The Army Medical Services, Doctor O. Nordlander, in Stockholm, from the donation
Swedish physicians have given to enable Finnish physicians to study
in Sweden. This made it possible for me to enlarge my field of study
during a visit to Stockholm in the year 1946.

Helsingfors, February 1948.

The Author.

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INTRODUCTION

At birth a child is solely a product of the foetal development. The growth of its organs has so far only been determined by the laws governing this. It has as its aim the bringing of the organs of the individual into a state corresponding to the demands of an independent life. They have not yet been affected by the influences that are determinable for their physiological functions during extra-uterine life. However, at the same moment as the child is born a reorganisation of its life functions commences, which is in conformity with the demands of the new environment. For some of the organs this occurs in stages; the digestive tract gradually becomes accustomed to its function and to harbouring intestinal bacteria. The central nervous system and the sensory organs gradually attain the degree of perfection that characterises them when fully developed. Contrary to these, the reorganisation of the respiratory and circulatory organs takes place within a moment. If respiration does not occur within the minutes following upon birth then the child hovers between life and death. If, for any reason, the circulation remains uncompleted leading e.g. to a persisting ductus arteriosus or an open foramen ovale, then it often has fatal consequenses for the child. It is to be expected that the blood, which is functionally a part of both the respiratory and circulatory system, undergoes considerable changes at birth. Such is the case in fact, and LIPPMAN (1924), who has investigated the morphology of the blood during the first day of life says: "There are many facts, that cannot be satisfactorily explained on the theory, that the condition of the blood of the new-born is a result of the continuation of fetal blood formation. One cannot account for the rise in blood elements at twelve hours, for the high values, if due to

fetal activity, should be present at birth; but this is not characteristic of the blood at birth. The morphology of the blood at birth approximates that of the last part of fetal life, and the picture presented is far different from that seen at six hours and again at twelve hours».

SMITH (1945) points out that the prenatal morphological development of the blood partly strives to make the blood similar to that which the organism can use in extra-uterine life, but in addition another important factor makes itself partly felt, i. e. that the blood has to serve the foetus that lives under quite different physiological conditions than the extra-uterine organism. The blood at birth therefore offers many features that distinguish it from the blood later on in life. The blood during the first post-natal period shows signs of the great change occuring when the child's organism adapts itself to its new mode of life.

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EARLIER INVESTIGATIONS

The blood picture at birth and during the first day of life.

Numerous investigations as to the blood picture at birth and during the neonatal period have been carried out. In this connection it is not worth while dealing with the blood picture of the newborn in and per se. The values obtained by various investigators vary considerably, partly owing to the fact that different haematological methods have been used, and partly because the blood samples have been taken at different periods; or because some investigators have used umbilical blood, some venous or sinus blood, while others have used capillary blood. The time of clamping of the cord also influences the blood picture of the newborn infant. A description from larger works on newborn infants' haematology might be appropriate. Only investigations into the values during the first day of life are considered. Table 1.

The count of the red blood cells is mostly high, as shown in Table 1. At all events the values vary widely. This is reported especially by Andersen and Ortmann (1937), who criticise the assertion of a high erythrocyte value being characteristic of newborn infants in general. A high erythrocyte value is considered a heritage from the pre-natal period. Between the pre- and post-natal phase comes the birth, with all its changes for the child. It is worth mentioning that no information has been obtained as to the count of erythrocytes in the child immediately before birth. As long as the field of studying the oxygen requirements and oxygen economy in the foetus, and the factors regulating the foetus' erythropoiesis remains unexplored the newborn infant's count of red blood cells must be regarded

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Authors	Kind of blood Time at which the cord was clamped Time at which the blood was taken No. of children	Erythrocytes	Haemoglobin	Haema- tocrit	Mean corp- uscular volume resp. volu- me index
Elder and Hutchison 1895	Blood from the umbilical cord Er. 6 children Hgb 9 4 Leuc. 12 4	5.347 (6.750-4.100)	105.6 (115-95)	-	_
*) William- son 1916	1 day	-	23.25 g./100 e. c. blood (Adult 16.92)	-	_
Lucas, Dearing, Hoobler, Cox, Jones	Cord clamped after cessation of pulsations	-		ada Albani	-
and Smyth	1 day Sinusblood 16 children Capillary blood Er., leuc. 12 children Hgb. 13 children	5.650 (6.800-4.760) 6.080 (7.024-5.336)	124 (140-110) 130 (145-120)		
**) Mayers 1922	At birth 41 children	7.63	_	-	-
Lippman 1924	Capillary blood Cord clamped after cessation of pulsations (2'-4'). At birth (0-1 ½ hours after birth) Er. 41 children Leuc. 42 children Nucl. red cells 42 children	5.19 (6.44-4.12)		-	7

^{*)} Quoted by Waugh et colleagues. **) Quoted by Lippman.

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Mean corp- uscular haemoglob- in resp. colour index	Mean corp- uscular haemoglob- in concent- ration resp. saturation index	Reticulocy- tes	Leucocytes	Further remarks
-	_	_	17,884 (26,500-12,200) Lymphocytes 35- 40 per cent Neutrophils 55-65 per cent	Nucleated red cells 1:20—1:8 of diff. leucocyte count No relationship between Er. count and Hgb. value
-	-	-	_	_
	-	_	19,400 27,200-6,000)	Nucleated red cells: 1 per cent of diff. leuc. count in 52 per cent of the ca- ses. Variations in cell size. Larger and smaller cells
			15,500 (21,000-11,000)	numerous.
	-	-	-	No relationship between Er. count and Hgb. value
-	-	-	16,600 (29,600–7,600) Polymorphonuc- lears:	Nucleated red cells: 3.2 per cent (37.8-0) 523 (4,800-0.0)
			46.7 per cent (74- 27.2) 7,798 (18,500-2,823)	Anisocytosis: in all cases
			Lymphocytes: 44.7 per cent (67.2-21.2) 7,618 (16.680-1,647)	Poikilocytosis: often

(Cont.

Authors	Kind of blood. Time at which the cord was clamped Time at which the blood was taken No. of children	75 - 41 4	Haemoglobin	Haema- tocrit	Mean corp- uscular volume resp. volu- me index
Haden and Neff 1924	Sinusblood 11 hours 11 children	4.57 (Adult 4.74)	15.6 g. (= 100 per cent) (Adult 95 per cent)	-	106 µ ³ (Adult 96)
Forkner 1929	Capillary blood 1 day 13 children	5.963 6.992—5.080	20.49 g.	_	
Mitchell 1929	Capillary blood 1 day 69 children	5.676 (8.230–4.150)	120 (152–89)	62 (79–44)	1,29
Kato and Emery 1933	1—4 hours 31 children		18 g. (18.8–14.5)		
Merrit and Davidson 1933	Capillary blood 73 children Er. Hgb. 1 day Ret. At birth	5.95 (6.8-4.6)	23.4 g (27.5-17)		-

(Cont.)				
Mean corp- uscular haemoglob- in resp. colour index	Mean corp- uscular haemoglob- in concent- ration resp. saturation index	Reticulocy- tes	Leucocytes	Further remarks
36 777 (Adult 31.2)	31.2 per cent (Adult 32.5 per cent)		_	Nucleated red cells: Non occuring. Anisocytosis: oc- Poikilocytosis: curing Cell count higher in capillary blood than in sinus of newborns of older
-	_	1.91 per cent	24,945 (45,000-15,250) Neutrophils: 68.7 per cent (82.5-53.0) 17,450 (33,525- 8,628) Lymphocytes: 18.3 per cent (36.0-9.0) 4,338 (8,722-2,000)	Nucleated red cells: frequently. Anisocytosis: Occu- ring Poikilocytosis: Mo- derate
1.06	-	-		-
-	-	-	-	_
-	-	3.40 per cent (5.50-1.8)	-	_

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Authors	Kind of blood Time at which the cord was clamped Time at which the blood was taken No. of children.	Erythrocytes	Haemoglobin	Haema- tocrit	Mean corp- uscular volume resp. volu- me index
Martin and Evans 1935	At birth (1-2 hours after birth) 20 children (10 normal delive-	5.512 (6.875–4.670)	118 (140–102)	-	_
Mugrage	ries) (10 Caesarean inf.) Blood from the	5.633 5.381 4.86	121 114 17.14 g.	53.18	108,9 µ³
and Andre- sen 1936	cord before the pulsations ceased 40 children Capillary blood	5.78	23.2 g.	_	_
1937	1—12 hours Er. 17 children Hgb. 16 children Ret. 15 children				
Ross, Waugh and Malloy 1937	At birth 12 children	7.5–4.6	139-98	75-49	***
Andersen	Venous and ca-	5.21	17.44 g.	56,5	108,2 µ3
1937	pillary blood Within 24 hours after birth Er. 43 children Hgb. 33 children Hcr. 38 children		(24.84-13.25)	(78.5–42)	(115.5-99.8)
Wollstein 1938	1 day 25 children	4.8 (5.5–4.0)	23.9–22.4 g. 142–130		

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Mean corp- uscular haemoglob- in resp. colour index	Mean corp- uscular haemoglob- in concent- ration resp. saturation index	Reticulocy- tes	Leucocytes	Further remarks
_	_	_	-	Nucleated red cells occuring
35.1 γγ	32.2 per cent	-	-	-
40.7 yy	_	2.50 per cent	-	-
_	_	_	-	-
33.6 γγ (36.7–28.7)	31.0 per cent (33.1–28.5)	_	-	_
-	_	-	14,380 (19,250-10,200) Polymorphonuc- lears 72 per cent 10,368 Lymphocytes 24 per cent 3,456	_

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Authors	Kind of blood Time at which the cord was clamped Time at which the blood was taken No. of children.	Erythrocytes	Haemoglobin	Haema- tocrit	Mean corp- uscular volume resp. volu- me index
Guest, Brown and Wing 1938	Cord blood 34 children	4.8 (6.0–3.8)	17.9 g. (22–13)		113 µ ³ (124-90)
Hurwitz, Mulay and Scott Laza- rus 1938	Capillary blood 1 day 9 children	5,26	16.6 g.	61	115.9 µ³
Waugh, Merchant and Maug- ham 1939	Cord blood Hgb, Her 53 children C. C. 41 children	_	15.6 g. (18.72–11.86)	51.3 (61-41) = 108 per cent of the value for	-
Chuinard, Osgood and	Sinusblood 1 day	-	-	-	-
Ellis 1941	11 boys	4.66	17.39 g. =	46.09	1.04
	9 girls	4.65	17.01 g. = 123.3	45.60	1.04
Shapiro and Bassen 1941	Capillary blood Mean age 11.4 hours (Within 24 hours after birth) 35 children	5.53 (7.15–4.23)	19.8 g. = 135 (172–102)	-	-

primarily against the background of its own physiology and not against that of the foetus.

The high haemoglobin value is due to the large red blood cells in the new5orn infant and to the often high erythrocyte count. In this connection it is advisable to consider the differences between the

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Mean corp- uscular haemoglob- in resp. colour index	Mean corp- uscular haemoglob- in concent- ration resp. saturation index	Reticulocy- tes	Leucocytes	Further remarks
37.5 yy	33.3 per cent (35.9–29)	-	-	_
31.6 yy	27.2 per cent		-	_
	30 per cent	2.7 per cent	-	_
		(5.0-0.2 per cent)		
	_		-	_
1.05	1.01			
1.03	0.99			
-	_	2.3 per cent (4.7-1)	24,000 (43,250–12,100) Myeloid cells 70 per cent Lymphocytes 25 per cent	-

foetal and adult haemoglobin. When in the corpuscles the foetal haemoglobin has a greater affinity for oxygen than haemoglobin later on in life. This facilitates the uptake of oxygen by the foetal blood in the placenta. In addition the foetal haemoglobin is also more resistant to an alkali denaturation as pointed out by Körber already in the

year 1866. This property has been used by several authors studying various types of human haemoglobin. (v. Krüger and Bischoff 1925. BISCHOFF and SCHULTE 1926, BRINKMAN and JONXIS 1935, HAURO-WITZ 1930, 1935). BARCROFT (1933) has investigated the O. dissociation curves of mother and child and came to the conclusion that they have two different kinds of haemoglobin. The same result is obtained by Roos and Romijn (1938) in studying the CO₂ dissociation curves in cows, i. e. the foetal haemoglobin varies from the maternal. Darrow, Novakowsky and Austin (1940) found immunologically different haemoglobin types in mother and foetus. Perrier and Janelli as well as Haurowitz (1935) found a difference between the shape of the crystals of foetal and adult haemoglobin. HAUROWITZ (1935) and Mc CARTHY (1943) found the red cells of the child having greater O2 affinity in suspension compared with those of the mother, while the opposite is the case with haemoglobin solutions. Andersch, Wilson and Menten (1944) have examined the different haemoglobin types electrophoretically. During recent years solubility methods in the separation and identification of pure proteins have been widely used. KARVONEN (1948) has shown the applicability of these methods in his work on the solubility of foetal and adult sheep haemoglobin. HAUROWITZ (1930) reckoned the proportion of the foetal and adult haemoglobin of a newborn infant as 80:20. Throught (1932) proved that at least some part of the foetal haemoglobin is of foetal type up to 1½ months of age.

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Frequently occuring nucleated red cells are characteristic of the red blood picture. This is pointed out by not only the authors listed in Table 1. but also by Fehrsen (1903) who has found erythroblasts occuring up to the 13th hour after birth. König (1910) found normoblasts and megaloblasts in 92 cases out of 100. Slawik (1920) found erythroblasts of normoblast type and pointed out the presence of anisocytosis and poikilocytosis, which is also mentioned in Table 1. Krumbhaar (1923) occasionally found normoblasts to last up to 24 hours after birth. Wiechmann and Schürmeyer (1925) have also noticed nucleated red cells. An investigation by Agress and Downey (1936) has shown that the nucleated red cells amount to 13.5 per cent of the differential leucocyte count. In this material too anisocytosis is observed. Anderson (1941) has examined the cord blood for nuclea-

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ted red cells. For full-term infants the count was 7.3 per 100 leucocytes, and for prematures and foetuses higher.

Even with regard to the frequent occurrence of reticulocytes the blood of a newborn infant is different from that of adults. In addition to the values mentioned in Table 1. KRUMBHAAR has counted respectively 4.7, 4.5 and 4.3 per cent during the first 2—4—6 hours of life. Seyfarth and Jürgens (1928) find 1—1 ½ hours after birth 6.2 per cent reticulocytes in the case of 29 children, and 2 hours after birth 5.5 per cent in a material of 13 children. These authors too have found some normoblasts. Finally, Kato's (1932) large work is worth mentioning. He found only small changes during the first 36 hours. The average count for this period is 1.64 per cent (5.5—0.1).

It is obvious that the size of the erythrocytes is influenced by this frequency of young cells. As a consequence an increased diameter with anisocytosis is observed. As, however, the value of the average diameter is dependent on the method used for measuring the cells, there is no point in reproducing any figures here. All the authors who have measured the mean diameter in newborn infants emphasise its largeness. ENGELSEN had already in the year 1884 measured the diameter of the erythrocytes, and he supposed that the increased amount of haemoglobin in the newborns' blood is due more to the large erythrocytes than to their great number. WIECHMANN and SCHÜRMEYER found a diameter essentially larger with the newborn as compared with adults, and anisocytosis too. The authors attribute this finding to the presence of nucleated red cells. SILVETTE (1927) has carefully examined the mean diameter of 30 newborn infants within an average age of 25 hours. From his material it is evident that the increased average diameter runs parallel to an increased colour index. BÖRNER (1928) too, has found a large diameter with newborn infants and considers this the cause of the haemoglobin value being proportionally higher than the number of red cells present in newborn infants. He comes to the conclusion that the haemoglobin value of the ted blood cells per surface unit is constant for all ages. Heiszen and SCHALLOER (1928) found anisocytosis with a normal haemoglobin content in the cells. The authors consider the anisocytosis more as a sign of immaturity typical of the foetal phase than as indicating a

rapid haemopoiesis. VAN CREVELD (1932) found an increased diameter with anisocytosis in both full-term and premature newborn infants. HERNBERG (1941) has carried out an investigation into the size of the erythrocytes at various ages. In newborn infants he found a large diameter, anisocytosis and poikilocytosis. The average age of the children examined by him was, however, 7 days.

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With regard to the mean corpuscular volume and the mean corpuscular haemoglobin the values in Table 1. in many cases are much higher than those for adults. (HADEN and NEFF, MITCHELL, MUGRAGE and ANDRESEN, ANDERSEN and ORTMANN, FAXÉN, GUEST and his colleagues, HURWITZ and his colleagues, CHUINARD and his colleagues). The mean corpuscular haemoglobin concentration does not, however, vary much from that of adults. HADEN and NEFF have pointed out that the mean corpuscular haemoglobin concentration seems to be equal at all ages. HURWITZ and his colleagues have found the value to be less than that of adults, after, however, having examined only 9 children. GUEST and his colleagues, and WAUGH and his colleagues find a somewhat lower value for the first period of newborn infants than later on in their early days of life.

An examination of the leucocyte counts as given in Table 1. shows that the leucocyte count per volume unit of blood is higher than in adults. It is evident from the investigations by Slawik, Forkner, Kato (1935), Agress and Downey, Wollstein, Shapiro and Bassen that the percentage of granulocytes is high and that of the lymphocytes is low. Lippman finds at birth much the same polymorphonuclear cells as lymphocytes, and that later on the number of the former is increased causing a percentage decrease of the latter. — In the same way as in the red blood picture, there are also immature cells among the white blood cells.

With regard to the difference between the venous and capillary blood it is observed in Table 1. that Lucas and his colleagues and Haden and Neff have found higher haemoglobin and erythrocyte values in capillary blood than in venous. This is proved by Vahloust (1941) and De Marsh, Windle, Alt and Hills (1941). Andersen and Ortmann, however, disregard the difference in the values between venous and capillary blood. Findlay (1946) mentions that capillary blood gives somewhat higher values, but as this difference is quite

inconsiderable he ignores it and uses venous as well as capillary blood for the same test. Horváth and Hollósi (1935 a) found at birth the same number of erythrocytes from the cord vein as from heel puncture, the tests being taken from 10 infants born by Caesarean section. In a later work (1935 b) they found the lowest value from the umbilical vein compared to the umbilical artery while blood from heel puncture gave the highest value.

The observation that the time for clamping the cord influences the number of erythrocytes has been made by HAYEM (quoted by ENGELSEN) who, among 6 infants whose cords were clamped early, found an average value of 5.087, while among 8 infants, whose cords were clamped after pulsations ceased, there were 5.58 million red blood cells. Schiff (1892) found that the erythrocyte value of infants, whose cords were clamped early, was highest during the first day of life, while the erythrocyte value of infants, whose cords were clamped late, reached its maximum no sooner than the third or fourth day of life. Scipiades (1903) discusses the importance of the time for clamping the cord and comes to the conclusion proved by later accurate work of DE MARSH, ALT, WINDLE and HILLIS and of SELAN-DER (1945) i. e. that the blood which comes from the placenta when the cord is clamped late belongs physiologically to the infant concerned, but nevertheless can be regarded as a pathological burden on the circulation. HASELHORST and TRAUTVETTER (1929) have compared the erythrocyte values of infants clamped early with those of infants clamped after 5 min. and found in the first group an average value of 5.478, in the second 6.761 million erythrocytes 16-18 hours after birth. Kramann and Hoffmann (1939) found at the age of 24 hours 18 per cent more haemoglobin and 19 per cent more erythrocytes with 200 infants clamped late as opposed to 200 children clamped early. DE MARSH, ALT, WINDLE and HILLIS have found on the average 4.5 million erythrocytes and 15.7 g. haemoglobin in infants whose cords have been clamped after 30 sec. and the same with 25 infants whose cords have been clamped after the expulsion of placenta, while the latter already 20 to 75 min. after birth had a greater value than the former. Observations on these infants were extended up to their seventh day of life, and the values for the infants clamped early have all the time been less than of those clamped later. The

opposite is the case with the reticulocytes. In a work published later on, De Marsh, Windle and Alt (1942) have investigated the blood volume and haematocrit value of 18 infants clamped immediately at birth, and of 17 infants whose cords have been clamped after expulsion of the placenta. They found that the haematocrit value in the former during a period from 15 min. to 3 hours after birth is on an average 53 per cent, of the latter 61 per cent. The blood and plasma volume is respectively 313, 142 c. c. and 364, 137 c. c. Finally observations by Selander are mentioned. He has investigated 1) immediately clamped infants, 2) infants whose cords have been clamped after the ceasing of pulsations 3) infants whose cords have been clamped after expulsion of the placenta — and found the value in the two last mentioned groups higher both during their first day of life and during their first week. The values of the two last mentioned groups are somewhat similar.

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Changes in the blood picture during the first hours after birth.

After this description of the haematological conditions in infants at birth and during their first day of life further explanations are given on interesting matters in connection with this research, i. e. changes occuring in the blood picture soon after birth, or in the hours succeeding it. At first a brief summary is given of the observations made and then a discussion on the theories as an explanation of them.

In the year 1876 LÉPINE mentioned that an increase of the red blood cells takes place during the first day of life.

Dupérié (1878) counts the erythrocytes as follows: —

1	hour	after	birth	4.33
1 1/2		39	9	5.704
1st	day		*	4.898

BAYER (1881) — in whose work both the previously named authors are mentioned — has found the following values: —

5 m	in —	3/4 of	an	hour	after birth	4.41
3 —	3 1/2	hours				5.433
6 1/2	- 9	*				5.173
1st	day o	of life				5.110

BAYER, however, does not give any idea of the extent of her material nor of that of the other two authors — and has also omitted to state whether the observations are made successively on the same infants or if different infants of various ages have constituted the material concerned.

Krüger (1886) found that the haemoglobin value of the foetus never reaches the same level as that of a newborn infant some hours after birth.

SCHIFF writes in the year 1892 that the red blood cells are greater in number 2—3 hours after birth than later on during the first 24 hours of life.

ELDER and HUTCHISON (1895) state that a rapid increase of the blood values takes place during the first hours after birth.

AITKIN (1902), found the following erythrocyte values: -

	6.130			
1	hour	after	birth	6.450
12-24	hours		19	7.670

Even here more detailed information about the extent of the material is omitted.

In the year 1902 VIERECK pointed out that there is an increase in the erythrocyte counts starting immediately after birth.

Lippman (1924) is the first author who has systematically investigated the blood cells during the first day of life. He has used capilary blood from one and the same child. His values of the red and white blood cells are as follows: —

Age	Number of infants	Er.	Leuc.
At birth (0-1 ½ h.)	41	5.19	16.600
5—7 h.	28	5.66	21.000
11—13 h.	27	5.52	22.500
15—21 h.	30	5.38	21.200

	Neutrophil cells		Lymphocytes		
Þ	er cent	absolute	per cent	absolute	
At birth $(0-1^{-1}/_{2} h.)$	46.7	7.798	44.7	7.618	
5-7 h. after birth	52.3	11.425	36.4	7.890	

Horváth and Hollósi (1935 a) have investigated 10 Caesarean infants: —

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						Er.	Hgb.
At	birth	blood	from	cord	vein	4.2	79
	9		*	heel	puncture	4.2	79
2	hours	after	birth	9		4.6	85
6		10	19	3)	D	5.2	90
12	9	9	1)	3)	1)	4.9	90

In a later investigation (1935 b) the authors arrive at the following results: —

At	birth:			1. Er.	Hgb	2. Er.	Hgb	3. Er.	Hgb	4. Er.	Hgb
Blo	od fro	m core	d vein	4.500	88	4.120	84	4.390	88	4.300	91
9	9	9	artery	5.010	102	_	_		_	-	- Ormania
9		hee	l puncture	5.420	110	5.040	103	4.390	88	4.670	102
2	hours	after	birth	6.250	129	5.330	111	4.990	95	5.300	112
6		9		5.890	119	5.500	118	4.810	98	5.800	119
12	*	**		5.890	120	5.700	118	4.680	89	5.200	113

SACHS, LEVINE, GRIFFITH, HANSEN (1938) found the following values:

			Er.
1)	8 Caesarean	infants	
	Blood from	the cord	4.746
	9 9	heel puncture	141.
		30 min — 4 hours after b	irth
		(average 1 ½ h)	5.461
			Er.
2)	19 normal	leliveries	
	Blood from	the cord	4.747
	9 9	heel puncture	
		20 min — 14 hours after	birth
		(average 2 h. 40 min.).	5.791

The investigation is made in connection with a study on the iron and copper value in the blood of mother and foetus.

RASI and BOLLETTI (1938 a) investigated 10 children:1)

	Er.	Ret.
At birth	5.170	119.000
12 hours	6.250	280.000

The same authors report in a later examination (1938 b)1):

				Er. 5 children	Ret. 4 children	Diam. 5 children
1	h.	after	birth	5.25	97.500	7.88
12	h.	9	9	6.19	237.000	8.42

RASI and CELLEGHIN (1939) 15 children1):

	Er.	Hgb.	Leuc.
At birth	5.500	112	13.500
12 h. after birth	6.024	122	14.500

RÄIHÄ (1941) has investigated 10 infants in connection with a study on tissue metabolism with newborns. Capillary blood was used.

Haemoglobin1):	at	t birth	118
	4	hours	133
	8	10	131
	12	1)	127
	24	0	124

DE MARSH, ALT, WINDLE and HILLIS (1941) report the following results:

	25 children	Er.	Hgb.
Bloc	od from the cord (clamped		
	within 30 sec.)	4.56	15.90
13	from heel puncture		
	20—75 minutes later	5.57	18.94
*	from the cord (clamped after		
	expulsion of placenta)	4.42	15.64
1)	from heel puncture		
	20—75 minutes later	5.99	21.60

¹⁾ The mean values are counted from the authors' tables.

FINDLAY (1946) has investigated a number of infants at birth and afterwards. In his work the children being investigated during the first hours succeeding the delivery have been picked out from his table. They are 7. The first test is from the cord clamped immediately, before cessation of pulsations, the second is from a heel puncture or from the scalp veins within 1 \(^1/_2\)—7 hours, — on the average 4 hours — after birth (6 infants — the number of hours being omitted for the seventh child):

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Ha	cr. (5 children)	Hgb.	Er.
Blood from the cord $1 \frac{1}{2}$ -7 h. (on the average	50	116	4.5
4 hours) after birth	67	162	5.9

From the data given above it is evident that the erythrocyte and haemoglobin as well as the reticulocyte and leucocyte value varies greatly during the first period of the first day of life. The values obtained at birth are less than those some hours later. Various theories have been proposed to explain this rapid increase.

HAYEM is quoted by SCHIFF (1890) as follows: — »Le nombre de ces derniers globales (erythrocytes) ne dépend pas d'ailleurs uniquement de la perte aqueuse que l'enfant peut éprouver par suit de l'inanition des prémières heures: il est influencé également et surtout par la production plus ou moins abondant de nouveaux élements». He thus takes into consideration a blood concentration as well as a haemopoiesis. These two circumstances leading to an increase of the blood cells have been noticed by almost all investigators dealing with this problem.

DUPÉRIÉ as mentioned above, considered that the increase of cells is caused by haemopoiesis. — The presence of young red cells as well as white ones in the peripheral blood picture of the newborn infant — as described previously also supports the assumption of an active haemopoiesis. Fehrsen, as well as Pehu, Pigeaud and Noël (1937) have observed that the young red cells are most common during the first hours of life, afterwards they decrease. Cathala and Daunay (1908), on the other hand found an increase of reticulocytes soon after birth in 5 infants out of 8 examined; in 2 the value increased while it was the same in one. Rasi and Bolletti have found an in-

crease in the red cell count, the haemoglobin value, the number of reticulocytes, the degree of macrocytosis and of anisocytosis during the tirst day of life. They explain this as a sign of irritation of the bone marrow in connection with the birth, and the changes in life conditions of the infant caused by the birth. BÜNGLER and SCHWARTZ (1927) report that the blood picture of the newborn infant undergoes changes in a form of a crisis immediately after the delivery, and that the changes in the red and white blood picture take place in a similar way. There is a parallelism between the myelocytes and the normoblasts. They call it: "Geburtskrise im Blutbilde". This crisis corresponds to the changes observed in experimental animals, and in adult humans, as produced e. g. by the reabsorption of haematomas or by parenterally administered foreign blood or protein.

As mentioned before LIPPMAN has carefully examined the blood picture during the first day of life. He states that the polychromasia, poikilo- and anisocytosis are most prominent at 6 hours, at which stage the amount of nucleated red cells is also highest. The increase of leucocytes depends on an increase in the neutrophil cells, while the absolute amount of lymphocytes does not vary. These are signs of haemopoiesis and LIPPMAN is inclined to believe that the increase of the cells is due only to haemopoiesis, while, in his opinion, the blood concentration can be omitted altogether.

Kato, who has examined the reticulocytes in a large number of newborn infants, says: »During the first 36 hours of life there is a very great and rapid process of readjustment in erythropoiesis incident to the commencement of an independent life on the part of the infant. Thus it may be proper to speak of this period as that of erythropoietic readjustment, while the period which follows lasting approximately five days may be considered as that of gradual transition to the normal level». Kato finds no change in the percentage value of the reticulocytes during the first 36 hours of life. Unfortunately no absolute reticulocyte values are mentioned.

Shapiro and Bassen found a large number of nucleated red cells in the bone marrow during the first day of life. Later on they decrease and the same happens with the normoblasts and reticulocytes in the peripheral blood.

The blood concentration causing an increase in the cells is, according to Forkner, already mentioned by Lépine. Among older investigators this theory is held also by Elder and Hutchison, who considered the increase to be too rapid to be due to a haemopoiesis. Forkner mentions Aitkin as adopting this theory also. Viereck states after discussing the importance of the time of clamping of the cord: »Unmittelbar nach der Entbindung tritt der Einfluss der Abnabelungszeit zurück gegen des Wasserverlustes der regelmässig zu einer sofortigen relativen Vermehrung der Blutkörperzahl und zu einem entsprechenden Gewichtsverlust führt».

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RÄIHÄ has found a rich excretion of pyruvic acid in the newborn infant. He is inclined therefore to believe in this hypothesis as supported by the fact that there is a relative anoxia in the tissues of the newborn infant. He connects this anoxia with the formation of oedemas and acidosis which YLPPÖ (1919, 1924) found with prematures and newborn infants. The oedema and blood concentration with a relative increase of the haemoglobin value is therefore caused by anoxia and acidosis. RÄIHÄ believes the blood concentration to be caused by forming of oedema and not by a dehydration of the children as other authors claim who adopt the theory of concentration.

MILLER (1941) has examined the blood chemistry in newborn infants at birth (umbilical blood) and found that the blood values (blood sugar, non protein nitrogen, plasma protein, Na, Cl) might be typical of a shock without the infant suffering from it. Åkerrén (1945) has given a report on the state of shock of newborn prematures. This shock is considered an important cause in producing the concentration of blood.

Even other factors — besides the haemopoiesis and the blood concentration — have been mentioned as causing an increase of the number of the cells in the blood soon after birth. BAYER is inclined to connect the increase in cells with displacements of the blood cells between the body surface and the inner organs owing to changes in circulatory circumstances and the commencement of respiration.

DE MARSH, ALT, WINDLE and HILLIS, think the increase of cells is possibly due to contraction of the spleen causing an expulsion of

erythrocytes in the circulation. In a later research DE MARSH, WINDLE and ALT, however, attach importance to the fact that the blood volume when the cord is clamped late is greater than when clamped early, while the plasma volume remains constant (page 22). They therefore consider the plasma volume, when the cord is clamped late, will rapidly regulate itself, while the blood cell count and volume undergo a relative increase. The authors have, however, in an earlier work come to the conclusion that this increase also refers to infants clamped early, though the increase is smaller. The increase found by FINDLAY (page 26) is very great; the children investigated by him were clamped early. It is to be observed that blood from the umbilical cord has been used in the first test, while in the second blood from heel puncture, and in some cases blood from the skin veins was examined. In investigations by SACHS and colleagues and DE MARSH and colleagues blood from the cord is compared with blood from heel punctures. According to investigations by Hor-VÁTH and HOLLÓSI (1935 b) the difference in the counts of blood from heel puncture at birth and two hours later is far smaller than the difference between blood from the umbilical vein at birth and blood from heel puncture two hours later. These two last mentioned authors consider that labour pains cause an increase of the blood cells after birth, but also that this increase is partly due to the blood concentration. FINDLAY discusses the haemoconcentration as well as the haemopoiesis - avoiding, however, the giving of a definite opinion.

The most certain method of finding out whether a blood concentration takes place or not would be to measure the changes in the blood volume during the first hours after birth. This is pointed out already by Lippman. Haden attaches importance to the knowledge of the blood volume in considering the counting of the erythrocytes of newborn infants. But with the methods available it is hardly possible to measure the blood volume of a newborn infant at intervals of a few hours. A blood concentration is also shown by an increase of the plasma or serum protein value. Nor have the changes of the plasma protein during the first period after birth been followed. The values obtained from the only test made at birth or during the first day of life are as follows: —

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UTHEIM	1920	14	ch.	1920 14 ch. 1st day Refractometry	try	6.25 per cent
PLASS and MATTHEW	1926 15	15	*	The cord WU's method	por	6.18
NAESLUND	1931	20	*	Umbilical vein Refractometry	try	6.06 (7.26-4.90)
				(The mother		8.2)
		10	*	Umbilical vein Water cont	Water contents of blood	92.1 per cent
						(90.8-93.3)
				(The mother		89.8 per cent)
1) Andersch and						
OBERST	1936 25	25	*	The cord. Micro-Kjeldahl	lahl	6.4 (7.7—5.3)
BRUCH and MCCUNE	1936	-	*	The cord, serum sp. gr. (BARBOUR — HAMILTON)	A — HAMILTON)	1.0241 ± 0.0042
		12		1st day venous blood		1.0263 ± 0.0036
				Protein (MOORE's and v. SLYKE's formula)	's formula)	
		1		The cord,		5.88 ± 0.34
		12		1st day venous blood		6.61 ± 0.41
1) POMMERENKE	1936 40	04	*	Umbilical vein Micro-Kjeldahl	lahi	5.89 (6.31—5.46)
				(The mother		6.55)
HURWITZ, MULAY,						
SCOTT LAZARUS	1938			1st day Greenbergs mod. of WU and LING: alb $+$ glob $= 3.82 + 1.77$	and LING: alb +	glob = 3.82 + 1.77
DENZER, WEINER, REINER	1939	17	*	The cord Refractometry	etry	6.06 (5.15-7.43)
		17	*	1-2 days Refractometry	etry	6.03 (5.10-7.02)
MILLER	1941	22	*	The cord within 5 min. Micro-Kjeldahl	dahl	5.66
				(The mother		5.77)
TREVONOW, KASER				Birth Micro-Kjeldahl	dahl	5.70 土 0.45
PATTERSON and HILL				(Adult		6.94 ± 0.47

¹⁾ These authors are quoted by SMITH.

met.

It is evident that the values are low throughout, in spite of the method used. The water content, as investigated by NAESLUND, is high. The specific gravity of the blood serum in 7 children examined by Bruch and McCune is somewhat lower than in adults.

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A summary of literature on changes in the blood picture of a newborn infant during the period immediately after birth shows that the number of erythrocytes and the haemoglobin value increase during this time. This is obvious from most of the investigations dealing with the subject. RASI and BOLLETTI found, moreover, that the reticulocytosis and macrocytosis became more pronounced in the course of the first 24 hours. FINDLAY found an increase of the haematocrit value during the first post-natal hours. LIPPMAN as well as RASI and CELLEGHIN found an increase in the leucocyte value. The materials are, however incomplete, and the investigations often made in a haphazard way. As pointed out previously, blood from the cord was in some investigations compared with capillary blood. In most cases no uniform time intervals have been observed, or the time intervals have been long. These remarks do not imply any criticism of the investigations mentioned above. Their aim has mostly been to elucidate other problems than changes in the blood picture of newborn infants, which thus constitute an incidental finding. LIPPMAN's study is systematically done, and his material is sufficiently comprehensive. The time between birth and the age of 6 hours has, however, been overlooked. Räihä has observed regular intervals of time for determinations of haemoglobin contents. and taken the second test not more than 4 hours after birth.

The purpose of this investigation was originally to follow the erythrocyte and haemoglobin values immediately after birth. After it became obvious that these values show a steady increase, the investigations were extended to comprise the leucocyte and differential blood picture too. The increase of red blood cells also gave occasion

to count the reticulocytes; for a number of cases a differential reticulocyte count is made. The analysis of the blood picture has been supplemented by measuring the mean diameter of red blood cells and by haematocrit determinations. In some cases also, the resistance of the red blood cells to hypotonic sodium chloride solution has been determined.

Some of the erythrocyte, haemoglobin, reticulocyte and leucocyte determinations have been carried out both on venous and capillary blood, in order to ascertain whether the changes take place similarly in both kinds of blood. For a series of infants with cords clamped immediately after birth, erythrocytes have been determined. All the other investigations have been made on venous blood and on infants whose cords were clamped after the pulsation in the cord had ceased. — The intention was also to follow the variations of plasma protein so as to ascertain the role played by the blood concentration in the increase of cells. It proved, however, difficult to procure a sufficient quantity of blood as only the superficial skin veins were resorted to for the venous blood. The studies on plasma protein or, more correctly, on plasma nitrogen, have thus the character of preliminary investigations.

MATERIAL AND METHODS

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The material consists of 293 children. The first part of the work was carried out at the Institute of Midwifery in Helsingfors, while the major part of it was performed at The Women's Clinic, Maternity Department, University of Helsingfors. When choosing the children no regard was paid to their weight at birth, their condition after birth or the kind of delivery. It is obvious that the major part of the material is represented by full-term infants, vigorous at birth, who have passed through a normal delivery. Among the investigated children there are also premature infants and infants who, through some cause or other, suffered from asphyxia at birth or thereafter, children who were born by means of Caesarean section, forceps or breech extraction. The subdivision of the material will be explained later on in connection with the account of the results of the investigations.

The major part of the investigations were made with venous blood while a part of them were carried out with capillary blood. In some cases both venous and capillary blood samples were taken from one and the same infant. In each case the skin was dried with ether before samples were taken. The capillary blood was taken from the heel by cutting with a Franck's needle and the venous blood from the scalp veins, in some cases from the veins on the back of the hand or on the inner side of the wrists.

The counting of the erythrocytes and leucocytes was performed in a Türk's counting chamber. The erythrocytes were counted in a dilution of 10 cu.mm./2000 cu.mm. and Hayem's solution was used as the dilutive liquid. The leucocytes were counted in a dilution of 25/500 and a half per cent acetic acid solution without any dye added thereto was used as the dilutive liquid. 62 double samples of the erythrocytes and 69 double samples of the leucocytes were taken in a series of 13 infants. The values of these double determinations are to be found in Tables 24 and 31 on pages 72 and 94. The reticulocyte preparations were vitally stained with brilliant cresyl blue. 2000 cells were counted. The smears taken for the differential cell counts were stained by the

May-Grünwald-Giemsa technique. When making the differential reticulocyte counts, equal parts of blood and isotonic sodium chloride—brilliant cresyl blue solutions were mixed, and smears were made from this mixture.

In a preliminary series comprising 20 infants the haemoglobin determinations were performed with a Hellige haemometer, while the other determinations were carried out by using a Zeiss-Ikon haemometer. At the first Hgb-determinations made with the Zeiss-Ikon haemometer a dilution of 30 cu.mm./2000 cu.mm, for which the apparatus is standardised, was used for the blood-hydrochloric acid solution. It soon became apparent that the blood of newborn infants had a too high haemoglobin content for the scale of the apparatus and the haemoglobin content of every sample could not be determined. For this reason a dilution of 15/2000 was thereafter used for the determinations and half of the haemoglobin value was thus obtained. Fifty five infants were examined in this manner. In the spring of 1946 I had the privilege of having my haemometer standardised by Dr Enghoff at the Physiological Institution in Uppsala. It was then standardised for a dilution of 20/2000. The standard used by Dr Enghoff was 20.5 volume per cent O₂ = 100 per cent Hgb. As is known, the original standard for the haemometer is 16 g. Hgb per 100 c.c. blood = 100 per cent Hgb. The values obtained with these two standards naturally cannot be compared with one another. Altogether 81 double samples were taken in a series comprising 15 children. The values of the double determinations are to be found in Table 27 on page 82.

The cell measurements were performed with the same smears that were used for the differential cell counts. The measurements were made by means of an ocular micrometer. The insignificant degree of poi-kilocytosis did not enable one to make any discrimination of diameters of different length, wherefore only one diameter was measured. The average diameter was counted from 100 cells. In 11 preparations the values of 100 and 200 cells were counted, and the same value was obtained as a result. (The difference = 0.000±0.060).

For the haematocrit determinations the blood was sucked up and centrifuged in 5 cm long capillary tubes. A 1—1.5 per cent heparin solution was passed through the tubes and they were then dried. The heparin solution was prepared by Pharm. techn. Lab. Medica, Helsingfors. The 5 per cent solution was diluted with distilled water. The tubes were firmly screwed into a stand containing 8 tubes, constructed for this purpose. When screwing them fast both ends of the tube were closed with a rubber packing. This method is suitable, as the required blood quantity is small, and as the blood is not diluted with any anticoagulative that can partly cause errors when diluting, and

partly bring about changes in the size of the blood corpuscles and cause haemolysis. KATO (1940) has found that heparin, contrary to other anticoagulatives, causes changes neither in the size of the erythrocytes nor in their form, and FINDLAY (1945) has pointed out that heparin is an anticoagulative that does not bring about haemolysis of the foetal red blood corpuscles. The haematocrit tubes were centrifuged 45 min. in a Santasalo-Sohlberg centrifuge, S-S-1, having 3000 revolutions per minute. The length of the pillar of the blood corpuscles did not generally change after 20-30 minutes. The tubes had no grading the length of the blood corpuscle pillar and that of the whole blood pillar was read with a controlled ruler, subdivided in 0.5 mm divisions. Thus the samples that did not completely fill the tube could also be counted. It was usually possible to clearly discern the stock of white blood cells from the tightly packed red ones. All the haematocrit values were counted from double samples. However, in some solitary cases, if the one sample was lost the other one was considered alone.

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When determining the resistance of the red blood cells to hypotonic NaCl solution the total haemolysis has been checked microscopically. The difference between the various dilutions in the series has been 0.02 per cent.

When taking samples for plasma nitrogen determinations the blood was sucked up into tubes having 2 and 3 mm diameters and of approximately 11 cm in length. One end of the tube was drawn out into an approximately 2 cm long capillary point. The above-mentioned heparin solution was passed through the tubes and they were then carefully dried. They were closed by a rubber ring that stretched from one end to the other and centrifuged in a stand containing 20 tubes. Both this stand and the one for the haematocrit tubes were constructed for this purpose by the firm Santasalo-Sohlberg, Helsingfors. Immediately after the centrifugation the plasma was put into tubes by means of a pipette and thereafter once more centrifuged - and pipetted into new tubes if any bottom flocking was formed. The tubes and pipettes used for the plasma tests were each time washed with bichromatic sulphuric acid mixture and rinsed with distilled water, and acetone was passed through them. The plasma nitrogen has been determined by the Micro-Kjeldahl technique. In cases, where the quantity of plasma was sufficient, double determinations were made. The determinations were carried out in the Department of Medical Chemistry of the University1). For a minor number of children, the plasma protein was determined by the Biuret method.

¹⁾ I wish to express my thanks to the superintendent of the laboratory, Professor P. E. SIMOLA, for his help.

The reliability of the mean values obtained has been checked by calculating the mean error of the mean values according to the following formula:

$$\epsilon\left(m\right)=\pm\left|\sqrt{\frac{\sum\limits_{i=1}^{n}\left(a_{i}--m\right)^{2}}{n\left(n-1\right)}}\right|$$

a_i = the individual values

e r s n l

1

m = the arithmetical mean of the individual values

n = number of determinations

RESULTS

Preliminary tests: For a series of 20 infants, erythrocytes and haemoglobin were determined each half-hour by using capillary blood. The first test was taken at birth. To the result showing that the values rise after birth, only qualitative significance can be attached, and for this reason the values obtained will not be analysed in detail. The curves in fig. 1 have been drawn on the basis of these values. The values obtained are to be found in Tables 22 and 23 on pages 70—71. Fig. 1 shows that an increase of erythrocytes and haemoglobin starts at birth. This increase culminates 2—3 hours after birth, and after that the values decline slowly. The haemoglobin values increase relatively more than the erythrocyte values.

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The first test was henceforth taken within half an hour after birth; the second when the highest values were reached in the curves of Fig. 1, that is, two hours later; the third, after the lapse of another two hours. Most importance is attached to these three tests although further tests, in several cases, were taken at two-hourly intervals. A report will be given below on the results obtained.

Erythrocytes: The red blood cells constitute, together with the reticulocytes, the essential part of the study, to which the other investigations are supplementary. The results of erythrocyte determinations have been grouped as follows: —

- A. Venous Blood.
 - a. the entire material
 - b. normal infants
 - c. infants suffering from asphyxia
 - d. infants born by abnormal deliveries
 - e. premature infants

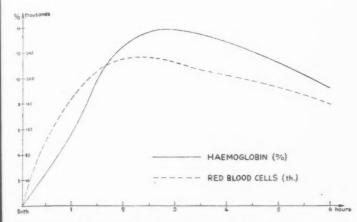


Fig. 1 is compiled on the basis of the values of half-hourly erythrocyte and haemoglobin determinations. Birth value is denoted by 0.

- B. Capillary Blood.
 - a. Cord tied late (after pulsations had ceased)
 - b. Cord tied early (as soon as the infant was born)

By way of explanation for this division, the following reasons are put forward:

As mentioned, preliminary investigations were made on capillary blood alone. When it became obvious that an increase in the values took place comparisons were made between values obtained from capillary and venous blood. It appeared that the values obtained when investigating venous blood showed changes characteristic of capillary blood. Consequently, only venous blood was investigated as the venepuncture provides more blood than the heel puncture. In most infants the cord was tied after the pulsations had ceased. For some of the infants, the cord was tied immediately after birth, and from these infants capillary blood only was taken for tests.

In respect of both capillary and venous blood, the results are calculated for the *entire number of children*.

As *mormal cases* are termed full-term infants delivered in the ordinary way, vigorous at birth and with no signs of asphyxia. The

*capillary blood cases include so few *abnormal infants that they can be overlooked, whereas infants deviating from the *normal* were so numerous among the *venous blood cases* that a breakdown of the cases became necessary.

As pasphyxia cases, were termed infants that for some reason proved conspicuously cyanotic at birth and retained the cyanosis longer than the few minutes it takes for a normal new-born to change colour from cyanosis to the rosy tint. In addition, pale infants with asphyxia are naturally included in this group.

In the group of *abnormal deliveries* such infants are included as were delivered by means of breech extraction, forceps, or Caesarean section. The detachment of a group like this is mainly due to the fact that the umbilical cord in these cases was severed earlier than in the case of a natural delivery. These infants were often in fairly deep narcosis when born, and respiration often did not start before several minutes had elapsed. These infants are also included in the previous group. This division is not a satisfactory one. The intention, however, has been, primarily, to investigate the changes in the blood picture of a normal new-born infant, but as there appeared a chance to add to the material with *abnormal cases* of this kind they were also taken into consideration, and the small group of *abnormal cases* was divided as stated above.

The last group comprises premature infants i. e. infants with a birth weight under 2500 grams. If a premature infant has suffered from asphyxia or been delivered by an »abnormal delivery», it has also been included in the above mentioned groups. A more detailed analysis of premature infants has been published previously (Wegellius, 1947).

The change in the erythrocyte values between birth and the age of two hours is elucidated below.

The value at birth is marked with I, the value two hours later with II. Table No. 2.

Table No. 3 shows the combined result of venous and capillary blood determinations for the same infants.

It is apparent from Table No. 2 that the birth value for the total material and for the normal material of venous blood is approx. 4.6 million. The dirfusion is small. The small groups of »abnormal infants»

Quality of blood Group of infants	No. of children	ı	E (I)	I—II∇	ε(□)	% ∇	€ (\(\nabla \))
Venous blood							
Entire material	117	4,587,000	十 44,000	+ 404,000	十30,000	* 8.8 +	+0.7%
(maximum-minimum)		(5,732; 3,144)		(+1,250,000; -680,000)		(+31.4; -14.0)	
Normal infants	7.9	4,577,000	± 55,000	+430,000	±37,000		₩ 8.0 ∓
(maximum-minimum)		(5,635; 3,144)		(+1,250,000; -416,000)		(+31.4; - 9.4)	
Asphyxia	15	4,487,000	± 71,000	+486,000	+45,000	+10.8%	+1 %
(maximum-minimum)		(4,880; 4,064)		(+704,000; +30,000)		(+15.7; +0.7)	
Abnormal deliveries	15	4,386,000	₹ 59,000	+284,000	干83,000	+ 6.5 %	±1.8 %
(maximum-minimum)		(4,870; 3,987)		(+693,000; +30,000)		(+15.7; -14.0)	
Premature infants	2.1	4,722,000	\pm 123,000	+342,000	±85,000	+ 7.2 %	十1.8%
(maximum-minimum)		(5,732; 3,530)		(+1,050,000; -680,000)		(+24.9; —14.0)	
Capillary blood							
Cord tied late	67	4,942,000	± 45,300	+354,000	₹38,000	+ 7.2 %	₹ 0.8 %
(maximum-minimum)		(5,744: 4,064)		(+1,017,000; -328,000)		(+22.5; - 6.3)	
Cord tied early	16	5,783,0001)	±127,000	+454,000	土75,100	±75,100 + 7.9 %	土1.3 %
(maximum-minimum)		(6.640; 5.120)		(+1,130,000; +180,000)		(+24.1; + 3.0)	

1) Cell counts are made by a different person from the one who made other counts and in another counting chamber (Bürker), for which reason value I for this group is not comparable with the other I-values.

TABLE No. 3.

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Quality of blood	No. of children	I	$\varepsilon(\mathbf{I})$	∆II–I	ε(△)	Δ%	$\varepsilon(\Delta^n,$
Venous blood Capillary blood	37			+ 349,000 + 358,000			

show somewhat deviating values. On the strength of this material, no difference can be proved between the various groups.

Capillary blood shows a somewhat higher value, approx. 4.9 million. From Table No. 3 it is apparent that no difference can be proved between venous and capillary blood as illustrated by this material, either with regard to birth value I or to \triangle II—I.

The increase from birth up to the age of two hours is distinct in each group. The values for the total material are increased by 404,000 up to 5.0 million, for the normal material by 430,000 up to 5.0 million. The increase represents in each case 9% of the original value. The infants whose cords were tied immediately do not differ from the others. Asphyxia cases show a somewhat higher increase while the values for the pahormal deliveries show a somewhat lower increase. As to the cases with asphyxia and the abnormal deliveries, it should be noted that 8 of the 15 cases appear simultaneously in both groups. The difference in the increase is due to the 7 remaining cases. For this reason, the 7 cases of each kind have been counted separately. Apart from that, the cases with asphyxia and the pahormal deliveries are counted as one group. The result is as shown below:

Group of children	△ II—I	Δ%
A. Asphyxia (7) B. Abnormal	+ 557,000	+ 12.1 %
deliveries (7) A+B (14)	$+\ 115,000 \\ +\ 431,000$	+ 2.6 % + 9.8 %

Here, it appears more distinctly that \triangle II—I for asphyxia is increased whereas, for the »abnormal deliveries», it is reduced. On the basis of these cases, no reliable conclusions can be drawn although it is unlikely that the result should be purely accidental.

In the following, the red blood cell values after time II (two hours after birth) are reported upon.

The time between 2 hours (II) and 4 hours (III): \triangle III—II is shown by Table No. 4.

TABLE No. 4.

Quality of blood	No. of childr.	A TITII	€(△)	Δ%	ε(Δ%)
l'enous blood					
Total material (MaxMin.)	57	$ \begin{array}{c} -169,000 \\ (-1,064,000 + 850,000) \end{array} $	±51,000	-3.3 %	±1.1 %
Normal infants	4.5	-175,000	$\pm 54,000$	-3.5 %	±1.1 %
MaxMin.)		(-1,060,000 + 850,000)		(-18.2; +20.1)	
Capillary blood	59	-273,000	±47,000	5.5 %	±1.0 %
Cord tied late		(-1.082,000; +330,000)		(-19.0; +6.4)	
l'enous blood and	30	-295,000	±49,000	-5.1 %	± 0.95 %
Capillary blood from the same	30	-337,000	±58,000	-6.4 %	±1.1 %

It is apparent from Table No. 4 that a small but distinct reduction can be ascertained between the ages of 2 and 4 hours and that consequently a peak appears in the blood cell curve (see Fig. 2) within 2 hours after birth. The changes in venous and capillary blood are similar to each other and do not, in extent, differ from each other.

Finally, a number of infants have been investigated at further intervals of two hours. These infants are combined into one group, and mean changes per two-hour periods have been calculated. It is natural that red blood cell counts do not change at a uniform rate during time intervals chosen at random, but a calculation made in this way is likely to give a picture of the direction the variations

TABLE No. 5.

Venous Blood	No. of children	△ N—II per 2 hours	€(△)
Total material	26	-79,000	±48,000
Normal infants	19	-63,000	±63,000

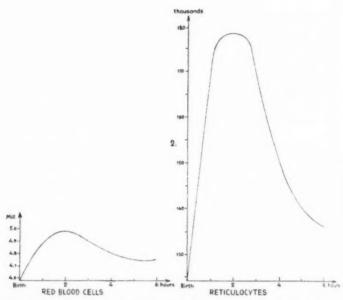


Fig. 2 discloses the changes in erythrocyte and reticulocyte counts. The graduation is chosen so as to illustrate the difference in the percentage increase.

in blood cell counts would have if a systematical change were discernible during this time. \triangle III—II is excluded from this group. The result is as shown by Table 5.

N in the Table stands for an age of 10 hours. Any systematical change of the values cannot be noticed on the basis of this material.

Although it exceeds the scope of this investigation, a small number of the children have been followed once in the 24 hours after the first 24 post-natal hours. The difference between the first (value III) and second 24-hour-period is, for total material of venous blood,—271,000 \pm 94,000. Graphic presentation of the course of the blood cell curve, based on the values obtained, is given in fig. 5.

A complete Table of the values obtained when determining the erythrocytes, is to be found on page 72.

Reticulocytes: As regards the division and treatment of the material, reference is made to what is said above of erythrocytes. As

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erythrocyte values vary at the various times when reticulocytes were counted, absolute values of the reticulocyte figures have been calculated. Variations in the values obtained, consequently, represent the variations in the absolute number of reticulocytes in the circulation, and not the proportional changes of the reticulocytes in relation to the number of erythrocytes. Table No. 6 presents the changes of reticulocyte values from birth (I) up to an age of two hours (II). The values stand for the number of reticulocytes per cu.mm.

TABLE No. 6.

Quality of blood. Group of children	No. of children	I	ε (I)	∀11 —I	$\varepsilon\left(\triangle\right)$	Δ%	ε(Δ%)
Venous blood							
Total material	66	124,000	± 8,000	+ 54,000	± 6,000	+44 %	± 5 %
(maxmin.)		(312; 10)		(+200; -34)		(+310;-25)	
Normal infants	42	126,000	±11,000	+ 58,000	± 8,000	+46 %	± 6 %
(maxmin.)		(312; 10)		(+200;10)		(+310;8)	
Asphyxia	12	134,000	$\pm 20,000$	+ 69,000	$\pm 16,000$	+ 52 %	±12 %
maxmin.)		(273; 21)		(+190; +17)		(+124; +11)	
Abnormal deliv.	10	96,000	土16,000	+ 37,000	$\pm 10,000$	+39 %	±10 %
maxmin.)		(172; 21)		(+182; +3)		(+124; +3)	
Prematures	12	105,000	土13,000	+ 32,000	± 8,000	+30 %	± 8 ° 0
(maxmin.)		(187; 45)		(+85; -8)		(+91;-25)	
Capillary blood	22	209,000	±12,500	+107,000	±15,000	+50 %	± 8%
maxmin.)		(373; 153)		(+224; +8)		(+129+8)	

Table No. 7 contains a comparison made between venous and capillary blood of the same children.

TABLE No. 7.

Quality of blood	No. of children	1	ε (I)	∆II—I	€ (△)	Δ%	€ (△%)
Venous blood Capillary blood	19 19	180,300 203,300		+102,000 +100,000			±6.7 ±6.9

As it is customary to indicate the reticulocytes as a percentage of red blood cells, the *percentage of reticulocytes* has also been calculated.

		Venous	blood		
Age	Normal material	As- phyxia	Abnormal deliveries	Pre- matures	Capillary
I	2.8 %	3.0 %	2.2 %	2.2 %	4.4 %
II	3.7 %	4.1 %	2.8 %	2.7 %	6.2 %
$\triangle II$ —I	0.9 % =	1.1 % =	0.6 % =	0.5 % =	1.8 % =
	33.3 %	36.7 %	27.3 %	22.7 %	40.9 %
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The changes taking place between the ages of 2 and 4 hours are as shown in Table No. 8.

TABLE No. 8.

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Quality of blood	No. of children	∇111–11	€(△)3	△%	ε(Δ%)
Venous blood					
Total material	33	-34,000	$\pm 11,000$	-16 %	±5 %
(Maxmin.)		(-189; +70)		(-49; +55)	
Norm. material	24	-39,000	$\pm 13,000$	-21 %	土7%
(Maxmin.)		(-130; +70)		(-40; +43)	
Capillary blood	14	-69,000	±15,000	20 %	±6 %
(Maxmin.)		(-135; +96)		(-38; -0.1)	
Venous blood and	13	-69,800	$\pm 16,000$	-23 %	+5%
Capillary blood	13	-68,000	$\pm 16,000$	-20 %	士5%
from the same					
infants					

The change between 2 and N hours, calculated by two-hour-periods, is shown in Table No. 9. \triangle III—II is excluded from this group.

TABLE No. 9.

Quality of blood	No. of children	△N-II per 2 hours	ε(Δ)	Δ%	ε(Δ%)
Venous blood	19	12,000	±4,000	-9 %	±3 %

N stands for an age of 10 hours.

A graphic presentation of changes taking place in reticulocyte values is to be found in Fig. 2.

As with erythrocytes, so also with regard to reticulocytes the values have been followed for a small number of infants during the first days of life. The results are presented diagrammatically in Fig. 6.

As a summary of the results obtained at the reticulocyte determinations, the following is worth pointing out:

For normal material, the reticulocytes amount to 2.8 % of the erythrocytes found in venous blood. After two hours, they will have increased to 3.7 %. As, however, the erythrocyte values have been subjected to changes, the absolute values of the reticulocyte counts have been calculated, and the same calculations have been carried out as with regard to red blood cells. It appears that the changes are qualitatively the same as in the case of erythrocytes although, as a percentage, they are considerably bigger. The increase in the absolute number of reticulocytes represents, at an age of two hours, 46 % of the birth value for normal material of venous blood. During the following 2 hours a fall of 21 % takes place. This fall continues from now on during the succeeding hours. — In this connection also, the asphyxia cases show the greatest increase, even if no demonstrable difference is discernible from this material. It can be mentioned that 7 cases are common to the asphyxia group and the »abnormal deliveries». The increase is least in the reticulocytes of premature infants but the cases are so few that no conclusions are permissible. — There is no difference discernible between venous and capillary blood.

The distinct increase of reticulocytes gave occasion to counting them in accordance with the Heilmeyer Scheme. The result is to be seen in Table No. 10. The number of cases analysed is 23. Absolute values of the percentages have been calculated.

At birth, Group $I + Group \, II$: Group $III + Group \, IV = 1:5$; consequently, a shift to the left is discernible in the reticulocyte picture.

Two hours later, the relation is I + II: III + IV = 1:4. Table No. 10 shows that a considerable increase of the youngest reticulocytes has taken place during the first two hours of life. The increase in Group I is 80 % of the initial value, while the increase in the other reticulocyte groups is approx. 30 %. A further shift to the left has

TABLE No. 10.

Group of reticulocytes	1	$\varepsilon(\mathbf{I})$	∇II-I	€(△)	Δ.0	E(4)
Group I	6,000	± 650	+ 4,800	± 800	+80	±1
(Maxmin.)	(15,000; 1,000)		(+20,000; -2,000)		(+630; -30)	
· II	15,600	$\pm 1,400$	+ 5,700	$\pm 1,900$	+37	2.13
(Maxmin.)	(29,000; 5,000)		(+23,000;6,000)		(+596; -29)	
· III	30,500	$\pm 2,300$	+ 9,300	$\pm 1,900$	+31	- 1
(Maxmin.)	(56,000; 15,000)		(+35,000; -4,000)		(+223; -8)	
. IV	68,300	$\pm 5,300$	+16,600	$\pm 4,300$	+24	2
(Maxmin.)	(119,000; 27,000)		(+65,000; -33,000)		(+153; -31)	

thus taken place. After this increase, no systematic change in the reticulocyte groups can be observed. A diagram illustrating the change of the reticulocyte values compared with that of the erythrocyte values is to be found in Fig. 2, and a diagram illustrating the change in Group I compared with that of the total number of reticulocytes is found in Fig. 3.

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A Table (25) showing the individual reticulocyte values is given on page 77. Differential count: Table 26 on page 81.

Haemoglobin: For reasons mentioned on page 35 above, during the first half of the work, the haemometer has been used for one half of the blood quantity only. The standard was 100 % = 16 grams/100 c.c. blood. Later on, a new standard was determined at which 100 % = 20.5 vol. % O₂. The values obtained when using the different

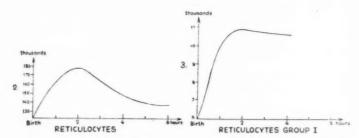


Fig. 3 shows the changes in the total number of reticulocytes and reticulocytes belonging to Group I. The graduation is chosen so as to disclose the difference in the percentage increase.

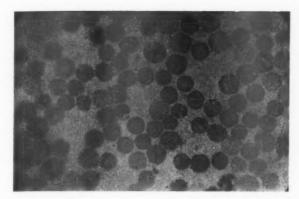


Fig. 4 presents a photomicrograph of a smear stained with brilliant-cresylblue. The picture reveals the round regular shape of the red cells, the anisocytosis, the profuse number of reticulocytes and their various stages of development.

standards are marked with H I and H II, respectively. The number of abnormal cases was so small that they have not been separated from the H I Series, whereas a number of premature infants are separated from the H II Series. Other infants deviating from the normal were so few in the H II Series that they have been ignored. The result for the time I—II is seen from Table No. 11. The value obtained when using H I has been multiplied by 2 (see page 35).

TABLE No. 11.

Haemometer, Quality of blood. Group of children	No. of children	I	ε(I)	△II-I	ε(Δ)	Δ%	ε(Δ%)
H I Venous blood (Maxmin.)	43	119.2 (154;86)	±2.2	+ 26.0 (+ 57;-2)	±2.6	+21 (+46;-3)	±2.2
H I Capillary blood (Maxmin.) H II Venous blood	48	127.6 (154;84)	±1.8	+ 21.6 (+ 23;-4)	±1.6	+17 (+50;-13)	±1.2
A. Total material (Maxmin.)	77	117.0 (150;55)	±2.3	+ 19.9 (+ 115;-14)	±2.3	+17.9 (+101;-11)	±1.9
B. Prematures (Maxmin.)	17	124.7 (152;91)	±4.5	+14.8 (+40;-8)	±3.7	+11.9 (+37;-5)	±3.0
A-B	60	114.8	±2.5	+21.4	±2.7	+18.7	±2.4

In the following Table (No. 12), venous and capillary blood from the same infants are combined.

TABLE No. 12.

	No. of children	I	ε(Ι)	∆II-I	ε (△)	Δ%	€ (△°)
Venous blood Capillary blood	36 36	120.8 128.8	±2.6 ±2.4	$+23.8 \\ +22.2$	±1.6 ±1.8	+19.7 % +17.2 %	±1.3 %

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If the values are calculated for g./100 c.c. blood, or vol. $^0\!\!/_0$ $\rm O_z$ respectively the results are: —

H I venous blood
$$19.0 \pm 0.4$$
 g. $+ 4.2 \pm 0.4$ g. $+ 3.5 \pm 0.3$ g. H II venous blood Group A—B $23.5 \pm 0.5\%$ 0₂ $+ 4.4 \pm 0.6\%$ 0₆

The infants examined between 2 hours and 4 hours of age come primarily under Group H I. The result is shown in Table No. 13.

TABLE No. 13.

ні	No. of children	∆III-II	ε(Δ)	Δ%	ε(Δ%)
Venous blood	36	-12.8	±3.0	- 9 %	±2 %
Capillary blood	41	-15.8	+2.4	-10.5 %	±1.6 %
Venous blood and	31	-14	+3.4	- 9.5 %	+2.3 %
Capillary blood	31	-15.2	±3.2	-10.1 %	+2.1 %
from the same infants					

Only a few tests were made with H II during the time II—III. For this reason, all the tests taken from time II onwards were combined, and the mean change for two-hourly periods calculated, as described above, with regard to erythrocytes. The result is to be seen in Table No. 14.

TABLE No. 14.

H II Venous blood	No. of children	△ N-II per 2 hours	ε (△)
Total material	49	+ 1.7	± 1.9
Prematures	12	- 1.5	+ 3.3

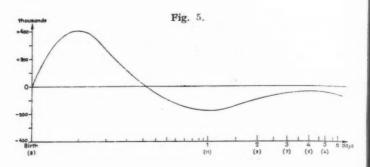
N stands for an age of 10 hours.

As can be seen from this, no systematic change takes place. Since, as shown by Table No. 13, a distinct fall between time II and III is discernible, the result is due to the fact that the fall of the values ceases after III. The 24-hour-curve seen in Fig. 7 assumes, however, the same form as the erythrocyte and reticulocyte curves, that is to say, the value for the second day is much lower than that for 4 hours after birth. In view of the fact that, as previously mentioned with regard to the 24-hour determinations of erythrocytes and reticulocytes, the number of infants observed during their first days of life is small, and because the 24-hourly determinations come outside the range of this study, no tables have been compiled for them, but results are presented only in the form of diagrams. Taken individually, they have no value on account of the scarcity of the material; as, however, all three of them seem to reveal the same course, the results support each other, and it therefore seems justifiable to take them into account. A Table illustrating the haemoglobin values is found on page 82.

Summing up, the following can be said of haemoglobin: the value at birth is high, 19.0 g./100 c.c. of blood, or 23.5 vol. % $\rm O_2$, respectively, which on the haemometer graduation corresponds to 119.2, or 114.8, respectively, in venous blood. After two hours, an increase of 17—21 % of the initial value takes place. As a percentage, this increase is considerably higher than that of the red blood cells. The value of the increase for premature infants is somewhat less, the difference, however, being uncertain, 5.1 % \pm 3.6 %. — After this, a fall of about 10 % takes place during the time immediately following. The next hours after this, again, show no perceptible change.

TABLE No. 15.

Venous blood	No. of children	I	$\varepsilon(1)$	△11-1	€(△)	Δ%	ε(Δ%)
Total material	52	7.63	±0.04		400.0	+3.1 %	-
(Maxmin.)		(8.3; 7.0)		(+0.9;-0.5)		(+13.7;-9.7)	
Prematures	12	7.56	± 0.1	+0.28	± 0.08	+3.7 %	±1.1 %
(Maxmin.)		(8.1; 7.1)		(+0.8; 0.0)		(+11.3;±0)	



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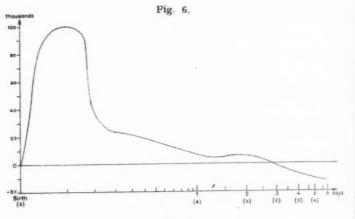
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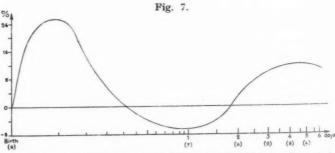
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Figures 5, 6, 7 show the changes in the number of red blood cells, reticulocytes and haemoglobin value during the first days of life. The figures in parentheses indicate the number of infants examined per day. Birth value = 0.

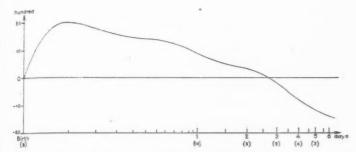


Fig. 8 shows the changes in the white blood cells during the first days of life. The figures in parentheses indicate the number of infants examined per day. Birth value = 0.

The mean diameter of erythrocytes: the fact that the increase of haemoglobin was bigger as a percentage than that of erythrocytes. gave occasion to studying the mean diameter of the red blood cells. The result is as shown in Table No. 15.

Total material
$$\triangle$$
 III—II for 21 children = $+$ 0.052 \pm 0.088 \bullet \triangle N—II per 2 hours for 55 children = $-$ 0.044 \pm 0.038

N stands for 10 hours.

In 17 tests, the diameter has been determined simultaneously for venous and capillary blood; no difference has been demonstrable. (-0.009 ± 0.033) .

The mean diameter at birth was 7.6 μ . During the first two hours the value was raised by 3 % whereas, during the hours immediately after that, it remained unchanged. The values of mean diameters are shown in Table 28 on page 88. — Anisocytosis was present in all cases, poikilocytosis in none.

The haematocrit value: Table No. 16.

TABLE No. 16.

Venous blood	No. of children	I	ε(Ι)	△II-I	€(△)	Δ%	ε (Δ%)
Total material (Max. min.) Abnormal de-	43	57.2 (69;40)	±0.9	+6.9 (+21;-15)		+12.1 % (+42;-25)	
liveries	8	58	+2.1	+1.5	+2.6		

Total material \triangle III—II for 13 children = + 0.6 \pm 0.9

• \triangle N—II per 2 hours for 37 children = - 0.4 \pm 0.4

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N stands for 10 hours.

The haematocrit value at birth was 57.2. Within 2 hours after birth the value increases by 12.1 % of the initial value, amounting to 64.1. No change takes place during the next hours after this. The material includes 8 abnormal deliveries, and these 8 infants show no increase. A Table showing the haematocrit values is found on page 91.

The mean corpuscular volume, C. V., the mean corpuscular haemoglobin, C. H., and the mean corpuscular haemoglobin concentration C. C. are calculated according to the formulas of *Wintrobe* (1932):

 $C.\ V. = \frac{\textit{Volume of packed red cells (in c. c. per 1000 c. c. blood)}}{R.\ B.\ C.\ (in millions per cu. mm.)}$

 $C.H. = \frac{Hgb \ (in \ grams \ per \ 1000 \ c. \ c. \ blood) \ (resp. \ vol \ ^0/_0}{R. \ B. \ C. \ (in \ millions \ per \ cu. \ mm.)} \ O_2 \times 10)$

 $C. C. = 100 \times \frac{Hgb \ (in \ grams \ per \ 100 \ c. \ c. \ blood) \ (resp. \ vol \ ^{\circ}_{\circ} \ O_{2})}{Volume \ of \ packed \ red \ cells \ (in \ c. \ c. \ per \ 100 \ c. \ c. \ blood)}.$

The mean corpuscular volume: The relatively low erythrocyte value combined with the high haematocrit value has given the mean corpuscular volume such a high value as $125 \pm 2.15~\mu^3$ at birth for 36 infants. Two hours later, the volume is found to be augmented by $+4.4 \pm 1.8~\mu^3$, equal to $3.6 \pm 1.4~\%$ of the initial value. The increase is thus not regular but present in a great part of the cases.

The mean corpuscular haemoglobin: The value for the first Series (H I) is = $41.4 \pm 0.54 \ \gamma \gamma$ at birth for 50 infants. Two hours later, an increase of $3.6 \pm 0.4 \, \gamma \gamma = 8.7 \pm 1.0 \, \%$ takes place. For H II the calculation is made with oxygen capacity as the unit. The corpuscular haemoglobin is in that case 54.2±0.9 vol. % O2 at birth for 56 infants. The increase after two hours is 2.7 ± 0.8 vol. % $O_2 = 4.9\pm1.5$ %. An increase of mean corpuscular haemoglobin can thus be observed. For pure haemoglobin solutions, 1.34 c. c. O₂ is equal to 1 g. Hgb. For H II also, in order to form an idea of the range of the haemoglobin present, in yy, the Hgb-quantity has been calculated according to this equation. The result is 54.2 vol. % $O_2 = 40.5 \gamma \gamma$ Hgb. The value obtained is, of course, not an exact one, as there is no question of a pure haemoglobin solution, but the value provides in any case an approximate idea of the haemoglobin quantity in $\gamma\gamma$. The value is in the same size class as that obtained with H I. - Neither corpuscular volume nor the mean corpuscular haemoglobin undergo any systematic changes during the hours succeeding the first 2-hourly period. The mean corpuscular haemoglobin concentration: Haematocrit determinations were made in the course of the latter part of the work while using H II. If oxygen capacity is taken as the standard, 42.8 % corpuscular O_2 capacity is obtained for 34 infants. \triangle II—I = + 1.45 \pm 0.88 and thus the concentration does not change. If concentration is calculated according to gram graduation, the value obtained for corpuscular haemoglobin is 31.9 %.

The resistance of red blood cells to hypotonic saline: As it is obvious that the number of red blood cells fell after the age of two hours, the resistance of red blood cells to hypotonic sodium chloride solution was investigated in some cases. This was done with a view to ascertaining whether the decrease was due to a decline in resistance. Out of this series, only those infants are taken into consideration where a decline in the number of red blood cells takes place:

Er. Total haemolysis 13 infants
$$-304.000 \pm 52.000$$
 -0.005 ± 0.0057

No change in the resistance against hypotonic NaCl solution is thus demonstrable. Table 30 on page 93.

Leucocytes: The number of infants deviating from the normal is so insignificant that they are ignored. The white blood cell count undergoes the following changes (Table No. 17):

TABLE No. 17.

Leucocytes	No. of children	I	ε(I)	∇11-1	ε(△)	Δ%	ε(Δ%)
Venous blood	51	11,700	±330	+1,530	±340	+13 %	1 2.9 %
(Maxmin.)		(20.6; 6.4)		(+8.0; -3.8)		(+72; -29)	
Capillary blood	20	14,100	±620	+2,450	± 530	+18 %	+4.0 %
(Maxmin.)		(21.3; 9.3)		(+6.8; -2.3)		(+73;-14)	
Venous blood &	19	12,900	±650	+2,580	±510	+ 20%	±4.0 %
Capillary blood from the same infants	19	13,900	±670	+2,490	±550	+18 %	±4.0 %

From two to four hours the leucocytes do not undergo any systematic change:

A small number of infants have been observed during the first days of life and the result is as shown in Fig. 8. The values for these infants have declined from the first to the second day.

The differential blood count: The changes in the total leucocyte count are due to changes in the number of neutrophil granulocytes and lymphocytes in a way shown in Table No. 18. As mentioned above with regard to reticulocytes, absolute values have been calculated for the percentages of the various groups of white blood cells.

TABLE No. 18.

Kind of cells	No. of children	I	ε(I)	∆II-I	€(△)	Δ%	E(A)
Stab neutrophils	23	555	±51	+ 264	± 62	+47.6%	±11.2
(Maxmin.)		(1070; 128)		(+862; -287)		(+238; -38)	
Segm. »	23	5000	± 265	+1650	± 336	+33 %	+ 6.7
(Maxmin.)		(7430; 2500)		(+5400; -570)		(+99; -16)	
Lymphocytes	23	5040	±253	970	±191	-19.2 %	+ 3.8
(Maxmin.)		(7020; 2860)		(-3360; +870)		(-50; +24)	

During the time II—III no systematic change can be observed.

Stab neutrophils	13	infants	-200 ± 75.2
Segmented »	13		-342 ± 477
Lymphocytes	13	35	-139 + 369

The percentage of neutrophil granulocytes and lymphocytes is as follows:

	I	II
Stab neutrophils	4.9	6.6
Segmented *	44.0	53.5
Lymphocytes	45.6	34.4

The absolute values of the neutrophil granulocytes show a remarkable increase during the first two hours, whereas the lymphocytes show a distinct drop, for which reason the increase percentage of the total leucocyte count becomes considerably lower than the increase of granulocytes.

Apart from these, the following kinds of cells are to be found in the blood picture, in the quantities given below:

	1		11	T
	%	abs.	%	abs.
Eosinophil granulocytes	1.7	192	1.4	170
Basophil	0.5	50	0.4	45
Myelocytes	0.3	33	0.2	26
Metamyelocytes	0.8	95	0.6	74
Monocytes	2.3	258	2.2	279
Macroblasts	2.3:400	60	1.8:400	51
Normoblasts	4.9:400	130	4.8:400	141
Plasmacells	0.7:400	4.5	0.09:400	3.1

These cells have been present in such small quantities that it has not been considered justifiable to encumber this study with a detailed analysis of them.

A diagram illustrating the leucocyte count is to be found in Fig. 9. In Fig. 10, the values of the neutrophil cells and lymphocytes are compared with the total cell count. Daily determinations of leucocytes are reported in Fig. 9.

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The values obtained for the total white blood cell count are included in Table 31 on page 94. The differential blood count is to be found in Table 32 on page 97.

Plasma nitrogen: At the time these investigations were carried out, the reagents for non protein nitrogen determination by Folin's method were not available. As, consequently, simultaneous values for non protein nitrogen were unobtainable, plasma nitrogen value has not been converted into plasma protein. The result of plasma nitrogen determinations is presented in Table No. 19.

The increase of plasma nitrogen is not present in every case but in the majority of the cases an increase of plasma nitrogen takes

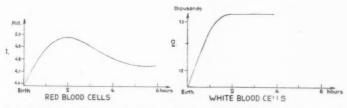
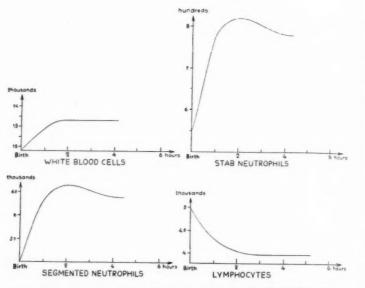


Fig. 9 shows the changes in the white blood cells compared with those of the red ones. The graduation is chosen so as to disclose the difference in the percentage increase.



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Fig. 10 illustrates the changes in the total number of white blood cells compared with the changes in the neutrophil cells and lymphocytes. The graduation is chosen so as to disclose the difference in the percentage change.

TABLE No. 19.

Plasma nitrogen	No. of children	I	ε (I)	△II-I	ε(Δ)	Δ%	€ (△,0)
Venous blood (maxmin.)		948 mg% (1,234; 574)		87.5 mg% (+546;—114)		+9.2 +95; —11)	±3.5

place. From reports published, the following values for neo-natal non protein nitrogen at birth and during the first day of life are compiled:

SLEMONS	1919	35	infants	24.9 mg %
Howe & GIVENS	1923	10	19	Cord 23.8 *
NAESLUND	1931	41	*	Umbilical vein 33.2 »
				(48.4-24.9)
SALMI	1935	38		Sinus blood 33.8 mg % (48-20)
				½-23 hours of age
BRUCH & MCCUNE	1936	5		per 24 hours 42.2 mg %
MILLER	1941			Cord 40 mg % (24-64)

SMITH estimates from the literature the non protein nitrogen at birth at 35 mg %.

Assuming that the non protein nitrogen at birth is about 35 mg% it seems highly unlikely that an increase of plasma nitrogen amounting to 87.5 mg% would be due to an increase in non protein nitrogen. The non protein nitrogen would, in that case, rise by over 200 % up to 122.5 mg%. SALMI finds that the value during the first 24 hours is 33.8 mg%, and BRUCH and MCCUNE ascertain a value of 42.2 mg% 24 hours after birth (only 5 children). — Plasma nitrogen increase of 87.5 mg% thus seems to be due, primarily, to the increase in plasma protein. In the cases where this increase takes place, it is thus to be assumed that a blood concentration takes place.

The change per each 2-hourly period from the age of 2 hours up to 10 hours is -25.6 ± 15.7 mg%.

For 10 infants, plasma protein has been determined according to the BIURET method (Table No. 20).

TABLE No. 20.

Plasma protein	No. of children	1	ε (I)	∆II-I	€(△)	Δ%	$\varepsilon \left(\triangle _{0}^{0}\right)$
Venous blood		6.7 % (8.0; 5.0)		+0.39 (+1.1; 0.6)		+5.8 (+30;-7)	± 3.3

The infants were few and the mean error big. As such, this result would be of no importance but as \triangle II—I takes a positive course, the results of plasma nitrogen and plasma protein determinations support each other. As pointed out above, no great significance is attached to these investigations as far as blood concentration is concerned. However, it seems justifiable to state that the result in no case precludes the existence of a blood concentration. The probability that a dehydration of blood takes place with a great part of the newborn infants during the first post-natal hours, is supported by the investigations. The values obtained are presented in Tables 33 and 34 on pages 100 and 101.

Weight. The 20 infants in the preliminary Series were weighed every half-hour. On the basis of these values, the weight at birth, at an age of 2 hours and 4 hours, was calculated. The result is seen from Table No. 21.

TABLE No. 21.

	No. of children	1	ε (I)	∆II-I	ε (△)	△%	€ (△%)
Weight	20	3420 g.	±100	—14 g.	±3.5	0.4	±0.1

When calculating the weight from the age of two to four hours, the value obtained is -2 ± 2 g. The decrease of weight during the first four hours is quite insignificant. The weights are presented in Table No. 35 on page 101.

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CONCLUSIONS

The outstanding feature of the material presented above is that a remarkable increase of cells in the peripheral blood takes place in the blood of a new-born infant within two hours after birth. A more detailed analysis shows the following:

The red blood cell count at birth is, in the present material, on an average 4.6 million. This value is rather low compared with those in Table No. 1. The variation is small. The table shows that the values at birth or afrom the cord usually are lower than in the investigations where blood is taken during the »first 24-hourly period» provided that the »at birth value» has really been determined at birth. LIPPMAN presents 5.19 as the value at birth, while the corresponding value as stated by MARTIN and Evans is 5.51. The values *at birth comprise here the values up to 1 ½ or 2 hours after birth. The low value and the small variation in the present investigation is due to the fact that the value at birth is determined within such a short period as half-an-hour after birth. Within two hours the increase is nearly ½ million up to 5.0 million. The increase is about 9% of the initial value. The count drops slowly after this. The increase ascertained by LIPPMAN and others thus begins with the delivery and reaches its peak about two hours later, from which time onwards the values gradually drop. LIPPMAN's peak for the red blood cells is fixed at 6 hours. He has made his second determination (6 hours) on the declining curve, when the values started dropping but still considerably exceeded those at birth. It was mentioned previously that SCHIFF had noticed that the value later on during the first 24-hourly period is lower than at 2-3 hours after birth. The haemoglobin value of the infants examined by Räthä is, similarly, higher at 4 hours than at birth and later on during the first day of life.

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As is evident from the present investigation, the increase in erythrocytes takes place side by side with a distinct reticulocytosis, The percentage of reticulocytes, for normal material, is at birth 2.8. The absolute value shows an increase after two hours, which. as a percentage, is about 5 times as great as the erythrocyte increase (40-50 % of the initial value). The youngest reticulocytes increase by 80 % of the initial value, while the other reticulocyte groups increase by about 30 % of the initial value. A distinct increase in young red cells thus takes place, and the reticulocyte picture with a shift to the left predominant already at birth (group I+II: group III+ IV = 1:5), experiences a further shift to the left. 1) CATHALA and DAU-NAY noticed an increase in reticulocytes during the first hours of life for five new-born infants. RASI and BOLLETTI found a higher value for reticulocytes at an age of 12 hours than at birth. — In this material the reticulocytes culminate at 2 hours after birth. The subsequent drop is about 20 %. The great increase and rapid decrease of the reticulocytes seem to give rise to the varying and often high reticulocyte values which appear in reports published.

In connection with the rapid increase of young red cells in the blood, the mean diameter of erythrocytes increases from 7.6 μ to 7.8 μ . — RASI and BOLLETTI have found a greater diameter 12 hours after birth than at birth. — That the increase is real and not due, for instance, to a change in pH, or to changes in the water content of the blood, or to a flattening out of the cells or something similar, is supported by the fact that the mean corpuscular haemoglobin content increases while the mean corpuscular haemoglobin concentration remains unchanged. The mean corpuscular volume is thus increased, a fact that is proved also, though somewhat irregularly, by the present calculations of the volume of the individual erythrocytes. As a function of the increased red blood cell count and of the increased volume and haemoglobin content of the new blood cells, both haemoglobin and haematocrit values rise. Both of

¹⁾ BOLLETTI and VILLANI (1947) report in a recent work a shift to the left in the reticulocyte picture at birth. 24 hours after birth a shift towards the right was found to have taken place.

these are high at birth. The haemoglobin value is $117 (100 = 20.5 \text{ vol.} \% \text{ O}_2)$ for the biggest group of infants examined. The value rises by 17.9 % of the initial value, reaching 136.9. This increase in haemoglobin is ascertained by Rähä and others. The haematocrit value, 57.2, increases by 12.1 % of the initial value to 64.1. Findlay has previously noticed that an increase of the haematocrit value takes place.

The red blood picture at birth obtained by the author is in its essential features in agreement with the blood picture obtained by others. The red cells are, however, unusually big; the haemoglobin concentration in the cells is normal. As regards changes after birth it is obvious that the results obtained previously by other investigators and described on page 22–26, in general features are confirmed by the results provided by the present investigation.

A definite increase of red blood cells in the circulation is considered to be caused by lack of oxygen. VAN LIERE (1943) distinguishes four different groups of oxygen lack or anoxia, viz. 1) anoxic anoxia or anoxaemia, 2) anaemic anoxia, 3) stagnant anaoxia, and 4) histotoxic anoxia. Most obvious here is the assumption that the infant, upon transition from the intra-uterine to the extra-uterine life suffers from anoxaemia, that is to say low oxygen saturation in the arterial blood, before the respiration and circulation have completely adapted themselves to the requirements facing them. That a relative anoxia actually prevails in the tissues of the new-born infant, is assumed by Räihä. It can be assumed that this anoxia in the tissues during the time immediately after birth is strong enough to cause such an increase in the red blood cells. The few infants suffering from asphyxia included in the present material, show a somewhat higher increase of erythrocytes than the others. EASTMAN as well as HASELHORST and STROMBERGER (1932) have found low oxygen saturation in the blood from the umbilical vein. Smith and KAPLAN (1942) have proved that a full oxygen saturation in the arterial blood is attained not later than 3 hours after birth. If the increase of red blood cells is meant to constitute a compensation for this insufficient oxygen saturation, the question presents itself why the new-born infant with its unsaturated arterial blood should need more oxygen carriers than the foetus with its unsaturated blood. Maybe the reason is that the foetus needs less oxygen

for its tissue metabolism than a being in extra-uterine existence or, that in spite of the low oxygen saturation in the blood if estimated according to adult standards, the foetal tissues might utilise the oxygen better than the tissues during extra-uterine life. For the needs of the foetus the oxygen tension of the foetal blood probably is quite adequate. The consumption of and demand for oxygen are probably heightened considerably when the foetal atonic muscles are suddenly transferred into a tonus and when the life functions of the child are activated after birth. — These are all questions that must remain unsolved until the demand for and economising with oxygen by the foetus and the new-born infant are analysed, and until the factors influencing the foetal haemopoiesis and those that regulate the blood cells in the post-natal circulation of the new-born infant are understood.

If one thus assumes that an anoxia is probably the cause for the increase of erythrocytes and reticulocytes after birth, the question that presents itself is which mechanism enters into operation at this juncture.

WINTROBE and SHUMACKER (1936) have proved, primarily by tests on animals, but also on humans that the farther the period of gestation proceeds the more numerous become the red cells and the less their volume and haemoglobin content, while the mean corpuscular haemoglobin concentration remains unchanged. Similarly, the content of immature cells is reduced. In the present case, both the number and size of cells are increased, as is the number of immature cells. The question can therefore hardly be of a continuation of the characteristics of the foetal blood formation during the hours succeeding birth.

BARCROFT (1927) has compiled the following schedule regarding the reaction of an organism against lack of oxygen:

	Emergency steps	
Possible methods for		
increase of red blood		
cell count		
	Final step	50

Dehydration
Opening of new
capillaries
Contraction of the
spleen
Unknown steps

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Activity of the bone marrow The rapid increase of erythrocytes and reticulocytes can hardly be assumed to be due to the fact that an increased formation of cells starts at birth. More probable is it that existing cells are released into circulation during the first hours of life. Shapiro and Bassen have actually proved that the bone marrow at birth is extremely rich in young red cells. It has been seen that already at birth the proportion between the young and older reticulocytes in the blood was 1:5. Forssell (1939) indicates the proportion for healthy adults as being 1:9 according to the Heilmever scheme. Two hours after birth, a further increase in the youngest cells can be ascertained. Existing reserves in the bone marrow are probably introduced into use, at the very outset.

When considering the various »emergency actions» BARCROFT lists, it seems justifiable to assume that each of these means to increasing oxygen carriers contributes to the final result. Although the present attempts at determining the fluctuations of blood concentration after birth are incomplete, they provide support to the theory of blood concentration. Micturition of the new-born babies has been extremely minimal during the time the present investigations were carried out. Most of them have remained dry all through the period, or just a drop of water has been passed during the first minutes. This quantity must have been present in the bladder at birth. SMITH indicates the quantity of urine excreted during the first 24 hours as being 15 c. c. No considerable excretion of water thus takes place during the first hours through the kidneys. The decrease in weight during the first two hours is practically non-existent and mostly due to meconium (14 g. = 0.4 %). No dehydration of the infant thus takes place. This would support Räihä's theory of formation of tissue oedema. Otherwise it seems probable that the water balance during these first hours is unstable with displacements both from blood to tissues and vice versa. Another factor to be considered is the apparent state of shock of new-born infants, as mentioned by MILLER and ÅKERRÉN (1945).

As regards opening the capillaries closed hitherto, it seems probable that, for instance in muscles extensive capillary systems are opened during the first hours. This gives occasion to displacements in blood between different parts of the organism which again may

influence the division of cells in the peripheral blood. The third of the emergency actions mentioned by BARCROFT is spleen contraction. There is hardly any doubt that at least a part of the increase of blood cells is due to a contraction of the spleen.

Finally it has to be pointed out once more that only an accurate knowledge of the oxygen metabolism, haemopoiesis, water economy, circulation conditions, in short, of the physiology of the entire organism at the time immediately preceding and especially after birth can supply the answer to the question of what are the reasons for such an exceptional physiological event as the increase of red blood cells in the peripheral blood and what is the mechanism of this occurrence.

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The decrease of the red blood cells after the initial increase is slight but perceptible. It is possible that the now superfluous surplus of red cells is gathered in blood reservoirs, in the spleen for instance. As a matter of fact, Åkerrén (1942) has found a palpable spleen during the first 24 hours of life in 40 infants out of a total number of 144 examined. Åkerrén assumes that this is due to a gathering of the now superfluous red corpuscles. In connection with this, also new displacements of the blood and of the red cells between various regions in the circulation can be considered. In the cases where the resistance was simultaneously tested, no reduction was found to take place. The decrease in reticulocytes is usually much bigger as a percentage (16—20 %) than that in erythrocytes. The simple explanation might be that the young cells mature in the circulation and are deprived of their reticulum.

The mean corpuscular volume, the mean corpuscular haemoglobin, and the mean corpuscular haemoglobin concentration do not change during the period following 2 hours after birth. The new big blood cells thus remain in the circulation during this period.

The value of the white blood cells is in normal material of venous blood 11,700, which is a fairly low value compared with those in Table No. 1. This value is considerably higher than the adult values. After two hours, the value has risen by about 1500 up to about 13,200. The increase is about 13 % of the initial value. No change is observed during the next two hours. A more detailed analysis of the white blood picture discloses that the neutrophil

granulocytes at birth represent 49 %, while lymphocytes amount to 46 % of the white blood cells. The absolute values are 5,600 and 5,000 respectively. The proportion of these groups agrees with that given by LIPPMAN, although his absolute values are somewhat higher. It is seen from Table No. 1, page 10 that other authors quote a much lower value for lymphocytes than for the neutrophil granulocytes. Two hours after birth, the values derived from this material are 60 % and 34 %, respectively, and the absolute values about 7.500 and 4,100, respectively. The change in the proportion between these two kinds of cells is partly due to the neutrophil granulocytes increasing, partly to the lymphocytes decreasing. In LIPPMAN's material, a corresponding change of percentage takes place but it is exclusively due to the neutrophil cells increasing (see page 23). About some hours after birth, LIPPMAN's values as well as those derived from the present material show greater compliance with the values obtained by other authors, who have taken their tests later on during the first day and not at birth.

The question of the reason for the changes in the white blood picture and of the mechanism for these changes, is left open here as a more detailed penetration into these problems, without thorough knowledge of the infant's physiology during this time, would only lead to fruitless speculation.

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SUMMARY

The red blood cell count of new-born infants in the peripheral blood increased from birth up to two hours after birth by about 9 % of the initial value. During the next two hours, the value dropped slightly; after that, no systematic change was observed during the succeeding hours. No difference could be found between venous and capillary blood; nor between infants whose cords were severed after the cessation of pulsations or those whose cords were severed immediately.

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The reticulocyte value increased during the first two hours of life by 40—50 % of the initial value, dropping after that by about 20 % during the next two hours. After that an insignificant decline could be noted during the succeeding hours. The reticulocytes were grouped according to the Heilmever scheme, and it was found that the increase for Group I, the most immature group, during the first two hours, was 80 % of the initial value, whereas the other groups increased by about 30 %. The initial reticulocyte increase is identical for both venous and capillary blood.

The haemoglobin value rose by 17—20 % of the initial value during the first two hours of life but dropped during the next two hours. During the following hours the values revealed no change.

During the first two hours, the mean diameter of erythrocytes increased by 3 % of the initial value.

The haematocrit value increased by 12 % of the initial value. The mean corpuscular volume and the mean corpuscular haemoglobin increased during the first two hours of life, while the mean corpuscular haemoglobin concentration remained unchanged.

No reduction in the resistance of the red blood cells to hypotonic saline solution took place along with the reduction in the red blood cell count.

The white blood cell count increased by about 13 % of the initial value during the first two hours of life. After that, no change in the count was observed. This material disclosed no difference between the changes in venous and capillary blood. A differential blood count showed that the neutrophil granulocytes increased by approx. 30 % of the initial value, while the lymphocytes dropped by about 19 %.

In the cases where the plasma nitrogen was determined, most of them disclosed an increase. The increase was about 7 % of the initial value and was assumed to be due to an increase in plasma protein.

The weight of the babies remained practically unchanged during the first 4 post-natal hours.

The results obtained have been briefly discussed.

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TABLE 22.
Red Blood Cells (in millions).
Capillary Blood. Preliminary Series.

			_	_		_				_		_	_	-	_					-
6 hours	5.043	5.511	4.802	4.900	4.858	5.093	1	1	1	1	1	1	*	****	1	1	1	1	1	
5 ½ hours	5.038	5.512	4.737	4.790	4.873	5.091	-	1	1	1	1	1	1	1	-	1	1	1		
5 hours	5.056	5.509	4.708	4.883	768.5	5.008	1	5.373		-	1	1	1	1	1	1	1	1	5.391	
4 1/2 hours	5.000	5.509	4.800	4.884	4.893	5.154	i	5.563	1	1	5.093	5.138	1	5.088	-	1	5.034	1	5.289	
4 hours	5.368	5.510	4.768	4.882	4.878	5.376	3.332	5.588	5.382	5.235	5.187	5.196	5.188	5.163	5.548	1	4.973	5.099	5,263	
3 ½ hours	5.472	5.518	4.992	4.883	4.839	5.056	5.350	5.578	5.570	5.197	5.136	5.200	5.099	5.098	5.555	1	4.980	5.127	5.273	
3 hours	5.363	5.548	4.734	4.899	4.890	5.024	5.240	5.587	5.561	5.189	4.936	5.146	5.192	5.132	5.572	4.987	5.087	5.132	5.311	5.521
2 ½ hours	5.496	5.320	4.784	6.909	4.905	4.672	5.328	5.585	5.587	5.209	4.840	5.132	5.272	5.200	5.521	4.925	5.240	4.938	5,045	5 620
2 hours	5.470	5.512	5.264	4.915	6.900	4.960	5.341	5.573	5.638	5.210	4.964	5.376	5.248	5.120	5.371	4.893	5.230	4.998	5.183	2000
1 ½ hours	5.560	5.592	4.856	4.903	4.830	4.920	5.256	5.572	5.624	5.123	4.724	5.520	5.288	4.832	5.593	4.878	5.018	4.937	4.973	2 2 2 2
1 hour	5.012	5.600	4.928	4.930	4.823	4.832	5.160	5.544	4.728	4.947	4.804	5.272	5.088	4.810	5.527	4.983	4.938	5.085	4.934	2 508
½ hour	4.960	5.300	4.712	4.890	4.880	5.009	5.272	5.256	4.938	4.931	4.760	5.198	5.143	4.751	5.231	5.088		5.273	4.832	2 4.01
Birth	4.560	4.888	887.5	4.836	4.789	5.135	4.836	4.913	4.936	4.821	4.936	5.231	5.184	4.632	4.880	5.098		5.331	4.897	2000
Child No.	-	. 81	60	4	10	9	1	30	6	10	11	12	13	14	15	16	17	18	61	06

TABLE 23.

TABLE 23.

Haemoglobin.

Capillary Blood. Preliminary Series.

Child No.	Birth	½ liour	1 hour	1 1/2 hours	2 hours	2 1/2 hours	3 hours	3 ½ hours	4 hours	4 1/2 hours	5 hours	5 ½ hours	6 hours
	16	100	101	116	116	107	107	106	110	100	100	100	
_	102	120	131	133	132	130	135	133	133	133	133	134	-
	06	103	100	97	120	120	118	110	100	100	100	100	-
	101	103	115	113	115	115	111	110	109	109	108	109	-
	66	110	112	112	115	120	117	117	116	117	117	118	1
	120	112	110	110	111	108	111	118	125	120	120	120	121
	96	102	105	115	120	120	120	121	121	1	1	-	1
	110	115	123	126	125	130	133	133	140	134	134	-	1
	112	110	102	135	137	133	133	132	133	1	1	-	1
	103	110	110	115	115	116	117	117	117	1	I	1	1
	110	100	115	110	112	110	115	116	116	116	1	1	1
	120	120	130	135	130	125	126	125	125	125	1	1	1
	110	105	106	110	109	110	110	110	110	1	1	-	1
	102	110	112	115	130	125	123	124	124	123	1	1	-
	102	120	130	130	128	130	131	130	130	-	1	-	1
	120	122	122	123	123	122	122	1	1	1	1	1	1
	1	1	115	116	120	120	116	116	116	116	1		1
	124	120	110	115	120	120	120	119	120	1	1	1	1
	113	110	115	118	125	122	127	125	124	124	124	1	1
	140	122	131	130	131	130	131	1	1	-	-	-	1

TABLE 24.

Red Blood Cells.

Venous Blood Normal Infants Capillary Blood
Cord clamped late

Ch

								pen susc	
Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours	Birth	2 hours	hour
21	-	1 -	_	_	_	_	5.472	6.020	1.96
22	-	-	_	_	40000	_	4.720	5.688	4.60
23	-	_	_		_		5.732	5.899	1.83
24	-	-	-	-	_	_	4.537	5.091	4.83
25	-	_	_	_			5.338	5.508	5.0:
26	_	_	_	_	_	_	5.135	5.527	5.3
27	5.635	5.510	5.510	_		-	5.531	5.213	5.50
28	5.593	5.732	5.437	_	_	_	5.581	5.781	5.33
29	-	-	-	_	_	-	5.372	5.721	5.43
30	-		_	-	_	-	5.132	5.831	5.23
31	5.280	5.537	4.531	-	_	_	5.152	5.500	4.4
32	4.793	5.130	4.389	_	-	_	4.639	5.231	4.36
33	5.372	5.538	4.937	-		-	5.193	5.516	5.0
34	4.813	5.530	4.891	_	_	_	4.766	5.500	4.73
35	4.637	5.361	4.530	_		-	4.521	5.538	4.53
36	5.317	5.589	5.261	_		_	5.289	5.539	5.38
37	5.504	5.888	5.538	_	_	_	5.489	5.893	5.5:
38	5.120	5.120	5.130	-	_	-	5.244	5.200	5.31
39	5.188	5.257	-	-	-	_	5.296	5.704	-
40	-	****	_	- 1		_	-	-	
41	-	_	-	-		-	5.537	5.544	4.96
42	5.131	5.229	4.816	_	_	-	5.003	5.312	4.95
43	5.024	5.072	5.003	-	_	-	5.320	5.152	5.13
44	4.448	5.032	4.998	- !	_	-	4.612	5.376	5.13
45	4.936	4.816	4.816	-	_	-	5.256	4.928	4.80
46	4.464	4.528	4.497	-	- 1	-	4.608	4.884	4.60
47	(4.464	4.582)1)	-	- 1	-	- 1	4.432	4.538	
48	(4.224	4.632)1)	-	_	_	-	4.440	4.716	-
49	(3.920	4.538)1)	-	-	-	- 1	4.064	4.662	-
50	4.192	4.460	4.512	_	-	-	4.368	4.728	4.57
51	4.368	5.037	5.200	-	_	_	4.624	5.138	5.46
52	4.592	4.640	4.544	-	-	-	4.714	4.880	4.68
53	(4.304	$5.008)^{1})$	-	-	-	-	4.512	5.184	-
54	-	-	-		-		_	-	
55	4.496	4.976	4.329	_		-	4.720	5.088	4.53
56	4.339	5.139	4.800	_	-	-	4.537	5.203	4.89

¹⁾ Belong to sabnormal groupss.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours	Birth	2 hours	4 hour
57	4.731	5.498	4.639	1	1_	1 -	4.759	5.538	4.79
58	4.836	5.399	4.889	_	-	-	5.003	5.476	4.99
59	4.420	4.720	4.420	_	_	-	4.504	4.992	4.663
60	4.196	4.480	4.227	_	_		4.480	4.704	4.33
61	4.886	5.410	5.007	-	_	-	4.937	5.476	5.030
62	-	_	-	-	-	_	4.672	5.436	5.26
63	4.656	5.152	4.660	-	-	_	5.408	5.538	4.74
	4.864	5.231	4.599	-	-	_	5.296	5.408	4.83
64	4.112	4.640	_		_	_	4.396	5.124	_
	4.040	4.664	_	-	_	_	-	_	
65	5.240	5.536	5.199	_	_	_	5.328	5.744	5.276
	5.128	5.520	5.338		_	_	5.272	5.632	5.140
66	_	_	_	-	-	_	5.744	6.064	_
67	(4.728	5.344	4.936)1)	_		-	4.784	5.216	4.938
	(4.768	5.388	4.971)			_	4.760	5.218	4.889
68	4.688	5.248	5.232		_	_	4.788	5.248	5.23
	4.664	5.344	5.057	_	-	_	4.700	5.120	5.318
69	4.384	4.320	4.640	-	_		4.892	4.810	4.816
	4.432	4.384	4.668	_	_	_	_	_	-
70	4.572	5.024	4.972	_	_	_	_	_	-
	4.588	5.039	4.999	-		_	_	-	_
72	4.532	4.949	5.147		_	_	5.040	5.286	5.120
	4.570	4.816	5.116	_		_	5.120	5.286	5.288
73		5.232	5.240	_	_				
		5.224	5.280	_	_	Child	Cord c	lamped c	arly
78	4.556	5.160	_			N.o 264	5.380	5.590	
79	4.612	4.934		_	_	265	5.400	6.700	-
80	4.760	4.960	_	_		266	5.120	5.300	-
83	4.578	5.000	_		_	267	5.800	6.560	
86	4.344	4.744	4.554		_	268	5.340	5.660	
87	3.840	4.594	4.352	_	_	269	5.690	6.200	
88	4.134	4.384	_	-	_	270	6.120	6.620	
89	4.136	4.532	-	-		271	5.350	6.170	
90	3.144	3.904	3.680	- 1		272	6.070	6.560	
99	4.512	4.852		_	_	273	6.640	6.920	
100	3.644	4.192	4.480	4.538	-	274	5.330	5.920	
102	4.416	4.000	-	-	_	275	6.180	6.500	
103	3.840	4.312		_	_	276	5.140	5.380	
106	_	4.384	4.352	_	1.132	277	6.360	6.680	
108	_	_	4.576	4.960	_	278	6.600	6.800	
-	elongs to	,			,	210	0.000	0.000	Wildred

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours	Birth	2 hours	4 hours
		1	1	1	1	1	1		
109	_	_	_	_	4.936	4.372	_		
110	4.128	4.608	-	-	_	-		-	-
118	4.096	4.862	-	_	4.544	_	-	_	
120	4.160	4.832	4.480	4.320	_		_		
122	4.224	4.768	-	-	4.530		_	_	
123	4.536	4.886	4.668	_	_	_		_	
125	4.160	4.820	_	_	_		_		
126	4.230	4.640	-	-	-	_			
129	_	-	_	5.950	6.280		-	-	-
130	_	_	4.830	_	5.670	_		_	
133	4.290	5.070	_	_	_	_	-	_	
135	_	5.480		5.380	_	_	_	_	-
136	3.850	4.070	_	_	_	-			-
137	4.610	4.870		_	_		-	-	_
138	_	5.250	_	_	4.840		_		
139	_	4.900	-	5.210	_	_	_		
141	4.480	4.810	4.920	_	_	_	_	_	
142	_	5.230	5.620		_		_		
144	4.820	5.540	_	_				-	-
145	4.740	5.190	_		_	_	_		-
146	3.920	4.690	-	_	_	_	_		
147	_	_		5.130	4.392		-	_	-
148	5.180	5.500	_		_		_	_	
149	4.710	5.430	_				_		****
150	4.980	5.160		_				_	-
151	4.590	5.580	_	_		_	******	_	
152	4.560	5,490	_		_	_		_	
154	5.320	5.640	_		_	_	_		
155		4.230	5.080	_					
156		5.790	6.000	_	_	_	_	_	-
157	3.930	5.070	0.000		_	_	_	_	
158	0.000	5.070	5.980	5.500	_				
160	5.120	5.530	3.300	3.000	_			mental .	
162	4.290	5.280						_	-
168	5.280	5.130		_	4.970				
169	3.200	5.690			4.570	5.560			
170	4.340	4.470		_		0.000			
175	4.600	5.410	_	_		5.070			
176	4.490	5.330	_		4.690	3.070			
184	5.460	5.440		-	1.090				
		200.00	_	_	_	_	-		
186	4.490	4.210	_		_	_	-	****	_

1)

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours	Birth	2 hours	4 hours
187		6.060	6.040	_	_	_	_	_	_
188	4.820	6.070	-	_	-	_	-	_	-
190	-	5.660	5.950		_	-			-
192	_	5.790	_	5.920	_	5.950	_		-
195	3.840	4.800		_	-		_		-
198	4.532	4.448	_		_	_			

Infants suffering from asphyxia.

		1	njants s	u/fering	from a	sphyxia.				
48	4.224	4.632			-	-	1 -		1	
53	4.304	5.008	_							l
67	4.728	5.344	4.936		_		_	_	_	١
	4.768	5.388	4.971	-	_			_	-	l
71	4.439	5.088	4.869	-	_		_	-	-	l
	4.399	5.136	4.857		_			_	-	l
74	4.848	5.120	4.820	_		-	_	_	_	l
	4.810	5.230	4.863	-	_		_		-	l
75	4.639	5.210	4.960	-		_		_	_	
	4.697	-		-	-		_		_	
76	4.524	5.130	_	_	-		-		_	
27	4.640	5.200							neces.	
	4.710	-	-		-		******	-	_	
98	4.160	4.800			-			-		
107	4.064	4.630	_		-	-		_		
112	4.480	4.736	_	-	-	-		_	-	
119	4.512	5.056	4.672		-		-	-	_	
140	4.880	5.220	-	_			-	-	_	
153		4.820	5.590	_		-	_			
161	4.200	4.230	_	_					-	
164	-	4.790	5.080		-					
177	4.870	5.400	_	_	_		_	_		

Infants born by abnormal deliveries.

1.7	4.464	4.582	- 1	-		-			
48	4.224	4.632	- 1	-	_			_	
71	4.419	5.112	4.863	_	-		-	-	
74	4.829	5.175	4.842		-	_	_	_	
1)76	4.524	5.130					-		
1)82	4.304	4.458	_		_	_			

¹⁾ Infants born by Caesarean section.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours	Birth	2 hours	hours
84	4.436	4.782		_	-	_	-		
107	4.064	4.630	-		-	_	_		_
1)112	4.480	4.736	_					-	_
119	4.512	5.056	4.672	1		_	-000-01		
1)131	4.330	4.570			_	-	_	-	_
159	4.260	4.540	_				_		_
161	4.200	4.230	-	-	-	-		_	_
166	4.870	4.190			-		_		_
1)185	4.280	4.630			-		_		

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours	Birth	2 hours	hours
23	5.732	5.899	4.835	_		_	_		
49	3.920	4.538	_	-	_	-			
85	4.278	4.830	_	_	_	_	_		
104	4.704	4.960		_		_			_
112	4.480	4.736	_	_	_	_			
124	4.450	5.470	-	_	tome.	_		_	-
127		5.850	5.190	_	_	_	_	_	-
134	4.670	5.540	_	5.050	-			_	-
163	5.230	5.500	_	-	_	_		_	-
164	_	4.790	5.080	_	_	_			
165	5.230	5.250	-		_	_		_	-
166	4.870	4.190	_	-	_	-			_
167	4.810	5.200			-	_		dam.	
171	3.530	3.890	3.830	-		_	_	-	_
172	4.440	4.600	4.720	-			_	A00000	-
173	5.410	5.700	_	5.030	_	_		_	
174	5.160	5.000	-	_	5.120	_	-	-	
177	4.870	5.400	-	5.360	_	5.330		-	
180	5.390	5.470	-		5.410	-	_		
181	4.220	5.270	-	_	5.250		_	-	
182	4.000	4.556	-		_	-		-	-
183	-		5.128	4.850	-				
185	4.280	4.630	-	-	-				-
189	5.480	5.710			_			_	-
191	-	4.480	4.850			_	-	_	-

¹⁾ Infants born by Caesarean section.

Daily values.

Child No.	4 hours	1 day	2 days	3 days	4 days	5 days	6 days
	1						
70	4.986	4.480	4.676	_	4.566	4.487	
	-	4.416	4.660	_	4.593	4.439	Nemen
71	4.863	4.792	4.560	-	4.648	4.928	
	-	4.768	4.608	_	4.552	4.939	-
72	5.132	4.544	_	4.722	5.184	5.072	5.286
	-	-	_	4.744	5.168	5.116	5.23
73	5.260	4.944	4.954	4.688	4.768	4.592	-
	_	5.036	4.860	4.724	4.808	4.454	_
74	4.842	4.288	4.288	4.486	4.416	_	
	_	4.240	4.288	4.439	-	_	
75	4.960	4.448	4.880	4.660	_	_	
	_	4.448	4.889	_	_	_	-
76	were	4.336	4.557	4.672	-		-
	_	4.320	4.556	4.699		_	_
86	4.554	4.472	4.384	_		-	-
87	4.352	4.408	4.448	4.138	_	-	_
88		4.228	4.112	4.008		_	-
89	-	4.580	_	_		_	

TABLE 25.

Reticulocytes (in thousands and per cent).

Venous Blood Capillary Blood Normal Infants

Child No.	Birth	hours	4 hours	Birth	hours	4 hours
16	312 7.0	367 8.2	342 7.6	373 8.1	415 8.5	363 8.2
47	_		-	315 7.1	354 7.8	_
48	(177-4.2	259-5.6)1)		213 4.8	255 5.4	_
49	(169-4.3	254-5.6)1)	Marine .	187 4.6	270 5.8	
50	168 4.0	259 5.8	221 4.9	179 4.1	278 5.9	243 5.3
51	236 5.4	292 5.8	354 6.8	264 5.7	303 5.9	399 7.5
52	197 4.3	223 4.8	218 4.8	222 4.7	239 4.9	234 5.0
53	(185-4.3	341-6.8)1)	-	203 4.5	368 7.1	
55	175 3.9	249 5.0	173 4.0	198 4.2	275 5.4	195 4.3
56	130 3.0	298 5.8	192 4.0	145 3.2	317 6.1	196 4.0
57	185 3.9	385 7.0	255 5.5	195 4.1	393 7.1	283 5.9

¹⁾ Belong to sabnormal groupss.

Child No.	Birth	2 hours	4 hours	Birth	2 hours	4 hours
58	247 5.1	383 7.1	298 6.1	260 5.2	394 7.2	340 6.
59	172 3.9	307 6.5	221 5.0	180 4.0	339 6.8	242 5
60	159 3.8	282 6.3	194 4.6	184 4.1	325 6.9	217 5.
61	186 3.8	368 6.8	320 6.4	202 4.1	400 7.3	322 6.
62	_		-	173 3.7	397 7.3	311 5.
63	195 4.1	275 5.3	181 3.9	257 4.0	306 5.6	201 4
66	-	-	_	247 4.3	438 7.2	
67	(147-3.1	209-3.9)1)	_	153 3.2	209 4.0	
68	177 3.7	228 4.3	180 3.4	157 3.3	218 4.2	
69	53 1.2	78 1.8	63 2.0	93 1.9	101 2.1	
70	128 2.8	211 4.2	155 3.1		_	
72	155 3.4	307 6.3	118 3.7	198 3.9	359 6.8	224 4.
73		115 2.2	142 2.7		_	-
100	44 1.2	59 1.4	_		Venous Blood	
103	31 0.8	43 1.0	_	6 hours	8 hours	10 hours
106	_	39 0.9	52 1.2		- 1	_
109	_	_	_		200.0	
118	33 0.8	92 1.9	_	_		-
120	33 0.8	96 2.0	58 1.3		76 1.6	39 0.
122	38 0.9	100 2.1	_		55 1.2	
123	73 1.6	122 2.5	84 1.8	43 1.0		
136	150 3.9	171 4.2	_	_	82 1.8	
137	175 3.8	195 4.0	_			
138	_	221-4.2	_	_	189-3.9	
139	_	157 3.9	_	_	_	
141	130 2.9	154 3.2	172 3.5	_	189-3.9	
142	_	220 4.2	315 5.6	203 3.9	_	
144	255 5.3	271 4.9		_	_	
146	161 4.1	225 4.8	_	_	_	
147	-	_	_	_	_	
148	93 1.8	105 1.9	_	_		
149	127 2.7	163 3.0	_	185 3.6	123 2.8	-
150	10 0.2	41 0.8	_			
151	73 1.6	123 2.2	-			
152	55 1.2	88 1.6	_			
154	74 1.4	73 1.3	_	_	_	
155	_	110 2.6	147 2.9			
157	39 1.0	95 1.5	-		_	_
158	_	_	168 2.8	-		-
		,				
1) D-1	ongs to as	shamis area		174 2.5		

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
160	31 0.6	50 0.9	_	_		-
162	60 1.4	105 2.0			eteros.	
168	190 3.6	180 3.5		_	124 2.5	Anna
169	_	114 2.0	_			100-1.
170	78 1.8	85 1.9				
175	138 3.0	168 3.1	-	-		
176	94 2.1	133 2.5		_	113 2.4	-
184	153 2.8	152 2.8	800000	_	_	
186	94 2.1	164 3.9		-	-	
187	_	170 2.8	157 2.6	_		
192	_ :	_	-	136 2.3		119 2.0

Infants suffering from asphyxia.

48	177 4.2	259 5.6	- 1			
53	185 4.3	341 6.8	_	****		
67	147 3.1	209 3.9	-		-	
71	119 2.7	189 3.7	141 2.9		-	-
74	116 2.4	134 2.7	102 2.1	-	-	
75	159 3.4	349 6.7	179 3.6	_		-
76	172 3.8	262 5.1	-		_	_
112	45 1.0	62 1.3			-	-
119	72 1.6	116 2.3	84 1.8	- 1	-	
140	273 5.6	303 5.8	-		_	-
153	_	106 2.2	168 3.0	_		-
161	21 0.5	47 1.1	-	-	_	*****
164	_	129 2.7	157 3.1			
177	127 2.6	167 3.1	-	3.0		-

Infants born by abnormal deliveries.

48	177 4.2	259 5.6	- 1	- 1	- 1	
71	119 2.7	189 3.7	141 2.9	-		enterior.
74	116 2.4	134 2.7	102 2.1	-	-	e-manufi,
76	172 3.8	262 5.1	- 1	-	-	
1)112	45 1.0	62 1.3		-		
114	-	44 1.0	_	34 0.8		-
119	72 1.6	116 2.3	84 1.8	-		-

¹⁾ Infants born by Caesarean section.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
1)159	60 1.4	64 1.4	*****			
161	21 0.5	47 1.1	Attentions	****		
166	93 1.9	96 2.3				
1)185	86 2.0	106 2.3				

169 4.3	254 5.6			-	- 1
45 1.0	62 1.3	-	-		
187 4.0	244 4.4	-	141 2.8	_	-
_	129 2.7	157 3.1	_		
47 0.9	58 1.1	- December 1	_	_	
93 1.9	96 2.3			_	
99 2.8	128 3.3	107 2.8	_	_	- 1
115 2.6	143 3.1	118 2.5	_	_	_
-	143 2.5	- 1	111 2.2		
139 2.7	105 2.1		-	133 2.6	
127 2.6	167 3.1		161 3.0		
156 2.9	148 2.7	-		130 2.4	- 1
80 1.9	153 2.9		_	131 2.5	
86 2.0	106 2.3				_
_	103 2.3	160 4.0		_	-
	45 1.0 187 4.0 47 0.9 93 1.9 99 2.8 115 2.6 	45 1.0 62 1.3 187 4.0 244 4.4 — 129 2.7 47 0.9 58 1.1 93 1.9 96 2.3 99 2.8 128 3.3 115 2.6 143 3.1 — 143 2.5 139 2.7 105 2.1 127 2.6 167 3.1 156 2.9 148 2.7 80 1.9 153 2.9 86 2.0 106 2.3	45 1.0 62 1.3 —	45 1.0 62 1.3 — — 141 2.8 187 4.0 244 4.4 — 141 2.8 — 129 2.7 157 3.1 — 47 0.9 58 1.1 — — 99 2.8 128 3.3 107 2.8 — 115 2.6 143 3.1 118 2.5 — 139 2.7 105 2.1 — — 127 2.6 167 3.1 — 161 3.0 156 2.9 148 2.7 — — 80 1.9 153 2.9 — — 86 2.0 106 2.3 — —	45 1.0 62 1.3 — <t< td=""></t<>

Daily values.

Child No.	4 hours	1 day	days	3 days	days	5 days	6 days
70	155 3.1	164 3.7	126 2.7		46 1.0	54 1.2	
71	141 2.9	-	142 3.1	min = 10	64 1.5	54 1.1	
72	118 3.7	105 2.3	_	62 1.3	57 1.1	51 1.0	89 1.
73	142 2.8	134 1.6	103 2.1	113 2.4	110 2.3	45 1.0	
74	102 2.1	47 1.1	43 1.0	49 1.1	44 1.0		_
75	179 3.6	93 2.1	171 3.5	140 3.0			
76	_	138 3.2	159 3.5	150 3.2	_		

¹⁾ Infants born by Caesarean Section.

TABLE 26.

Differential Reticulocyte Count
Venous Blood

Child No.	Age	Et.	Ret.	Group	Group II	Group III	Group IV
180	Birth I	5.390	2.9 %	1%	11 %	36 %	52 %
	2 hours II	5.470	2.7 %	4 %	11 %	35 %	50 %
181	I	4.220	1.9	7	22	37	34
	11	5.270	2.9	6	13	35	45
184	I	5.460	2.9	5	19	24	51
	II	5.440	2.8	5	14	30	48
185	I	4.280	2.0	7	19	30	43
	II	4.630	2.3	4	12	37	47
186	I	4.490	2.1	7	7	37	49
	II	4.210	3.9	5	18	30	46
187	II	6.060	2.8	3	10	37	50
	4 hours III	6.040	2.6	7	8	39	46
246	I	3.980	2.4	5	18	33	44
	II	4.980	2.9	10	21	26	43
	III	4.780	2.0	6	20	28	46
247	1	5.370	2.2	1	16	30	53
	II	5.980	2.4	6	10	29	55
1	III	5.580	1.7	6	8	26	60
248	I	5.550	2.5	4	6	21	68
	II	6.230	3.0	1/4	8	22	67
	III	5.900	2.4	2	8	26	64
249	1	4.910	1.9	6	10	31	53
- 1	II	5.770	3.1	7	9	20	64
	III	5.730	2.6	11	17	25	47
250	1	4.980	3.0	8	18	21	53
	II	6.180	3.2	16	13	23	48
251	I	5.590	1.4	4	7	20	69
	II	6.320	2.5	4	10	24	62
	III	5.960	2.2	4	11	18	67
252	I	5.010	3.5	2	9	21	68
	II	5.750	3.6	4	17	21	58
	III	6.350	4.4	4	12	31	53
253	I	6.400	2.8	5	13	24	59
	11	6.270	2.3	5	12	34	50
		6.700	2.5	5	12	22	62
254	I	6.250	1.3	6	17	21	57
	II	6.910	1.9	4	12	18	67

Child No.	Age	Er.	Ret.	Group I	Group II	Group III	Grou IV
255	1	5.090	3.7	5	14	20	61
	11	5.850	3.7	9	13	22	56
256	1	4.290	1.5	6	8	24	63
	11	5.020	3.6	8	19	28	46
	III	4.940	2.6	7	13	22	58
257	I	5.270	1.8	5	12	18	67
	11	6.030	2.4	9	13	17	62
	III	5.920	2.5	10	18	21	51
258	1	6.520	2.2	3	9	24	65
	11	6.260	2.4	7	16	22	56
	111	6.100	2.3	5	16	24	56
259	1	5.090	2.4	5	16	28	51
	11	5.460	2.5	6	18	26	51
260	1	5.080	1.7	5	15	18	63
	II	5.760	1.7	5	12	19	65
261	1	5.520	1.9	5	5	17	73
	II	6.010	3.0	7	13	22	59
	III	6.130	2.1	6	14	27	54
262	1	7.010	2.7	8	14	27	51
	II	6.940	3.0	13	14	25	49
263	1	5.150	1.8	9	14	27	51
	11	6.050	2.0	10	20	23	48
293	11	5.260	2.1	3	7	17	79
	III	5.920	2.6	2	5	17	77

TABLE 27.

Haemoglobin.

Haemometer I.

	Venous 1	Blood		Capillary Blood		
Child No.	Birth	2 hours	4 hours	Birth	2 hours	4 hours
21	_		_	55	65	58
22	-	mone	_	53	65	49
23	-	_	_	66	68	55
24	_			54	65	55
25	-			62	65	58
26	-	-	-	59	71	63
27	74	72	68	74	70	69
28	68	78	67	69	78	66

hild No.	Birth	hours	4 hours	Birth	2 hours	hours
29				68	75	69
30				64	80	71
31	66	77	53	62	75	52
32	63	75	58	61	75	56
33	65	72	43	64	71	45
34	58	72	53	55	70	53
35	43	63	40	42	65	51
36	63	71	53	62	70	52
37	66	74	72	65	75	70
38	61	68	69	64	75	75
39	65	71	_	76	85	_
41		_	_	74	80	70
42	59	70	74	62	71	82
43	59	77	80	72	86	82
44	55	69	70	61	81	82
45	67	79	78	73	81	79
46	60	73	68	68	75	71
47	_	_	_	63	68	-
48	55	69	_	60	72	_
49	48	65	_	51	69	_
50	50	65	60	57	68	62
51	57	72	80	61	74	88
52	65	67	69	68	76	74
53	60	79	_	64	82	-
55	56	67	65	65	70	67
56	56	70	62	60	72	65
57	66	80	67	67	82	70
58	74	83	78	76	85	80
59	58	76	60	59	77	63
60	54	70	56	64	74	60
64	63	80	75	65	82	76
62	_		-	65	81	78
63	67	78	67	71	82	72
	66	79	65	70	81	74
64	51	67		65	71	-
	59	69	_	64	70	-
65	77	84	76	78	85	77
	-	_		76	84	76
66	68			71	92	_
	68			_	91	
67	52	72	62	55	71	60

Child No.	Birth	2 hours	4 hours	Birth	2 hours	4 hours
	54	72	62	56	71	61
68	61	77	76	63	77	76
	61	78	77	62	75	77
69	51	50	58	72	70	7.0
- 1	49	52	59	71	70	_
70	59	69	64	_		_
	60	68	65	_	-	-
71	55	65	65	_	_	_
	53	65	64			_
72	56	70	76 .	69	79	77
	57	68	78	70	79	79
73	-	71	69	-	_	-
	-	71	70			
74	57	60	58			_
	56	61	59		_	-
75	56	74 .	70	-	_	_
- 1	54	-	69		_	_
76	54	68		- market		-
		68	-			-
77	47	63				
	48	63			_	-

Daily values.

Child No.	4 hours	1 day	days	3 days	days	5 days	6 days
70	64	61	67		60	53	
		60	66	_	60	53	
71	65	61	65		58	63	-
	-	61	64		57	64	_
72	77	65	-	57	57	64	70
- 1	-	66	_	58	67	65	69
73	69	57	63	67	65	62	_
		58	62	67	66	62	
74	58	47	51	52	49		
		46	51	52	50	_	
75	70	48	64	60			
- 1		49	64	_			-
76		49	57	57	-		
		49	57	55		_	-

Haemometer II.

Venous Blood.
Full-term Injants.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
78	111	121	_		_	_
79	99	138	_			
80	102	131			_	_
81	105	114				_
82	79	94	_		none.	
83	99	168	_			
86	128	114	142		-	
87	86	173	128	_	_	
88	79	99				
89	105	155	_	-	-	-
90	65	79			****	
92	93	114	_	_	_	
94	91	111	_			
95	55	89		-		
96	99	135		-		
97	118	128	-			-
99	119	138		-	-	-
100	-	_	126	155		
102	129	133	-		-	-
106	Wiles in	136	136	_	-	146
107	119	121				
108	-	_	181	199		
109		_			155	1.78
114	_	126	-	110		-
116	telling	-	129	155		
118	118	128	-		136	
119	118	119	123	-		-
120	142	164	166	173		tanga.
122	136	176	_		168	-
123	133	159	168	-		toda-
125	108	108	_			
126	101	135				-
129		-	_	173	176	-
130	-	_	138	_	148:	
131	104	118				-
133	107	126	_	-		
137	128	130	_		****	-

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
139	_	140	_	155		
140	150	184	_	100		
141	142	150	166			
142		181	187			
143	_	161		161		
144	128	171				-
145	126	150				
147	_	_	_	129	129	
148	123	135			140	
149	118	135	_			
150	136	142				
151	126	150		_		
152	126	159	_			
153		171	178	_	_	
154	148	168		_		
155	_	126	135			
156		178	171			
157	107	135	_			
158			168	155	_	
159	105	113				
160	95	119		_		
161	91	91				
168	136	136			-	
169	_	166	_		_	157
170	110	119				
175	123	148		_	_	131
176	109	142		_	129	
184	136	146	142	_	_	
186	123	138	_			***
187	_	152	173	_	_	******
188	131	148			_	
190	-	166	159	-	_	-
192	_	202		187	_	178
193	131	146		_	_	
194	128	146	-			
196	135	133	_			
200	133	168	-			
201	131	246	con a		-	
202	99	107	-			-
203	110	110				
205	_	133	_	121	_	

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
206	113	142	_			
207	113	140		_	-	
208		166	187	_		
209	131	136	_	-	-	_
233	******	-	114		124	
235		133	124			-
239	-	166		161		
240	same,	123	_		114	-
241		114		126	_	126

		U1111111111 210	1		
132	135	110		10.21	
96	130		-		
98	134	_	-		
144	184			_	-
144	164				
	164	159			****
150	178		159		
121	136	-	_		
	102	115	-		
152	144				
104	113			_	
126	157				
91	104	105			
126	146	124	_		_
131	126	-		129	
126			148	_	148
142		-	_	128	_
114		_			
123					
_		161	_	_	
		_	152		
	96 98 144 144 — 150 121 — 152 104 126 91 126 131 126 142 114 123	132 135 96 130 98 134 144 184 145 164 — 164 150 178 121 136 — 102 152 144 104 113 126 157 91 104 126 146 131 126 126 124 142 148 114 131 123 123 — 150	132 135 110 96 130 — 98 134 — 144 184 — 144 164 — — 164 159 150 178 — 121 136 — — 102 114 152 144 — 104 113 — 126 157 — 91 104 105 126 146 124 131 126 — 126 124 — 142 148 — 114 131 — 123 123 — — 150 161	96 130 — — 98 134 — — 144 184 — — 145 164 — — 150 178 — 159 121 136 — — — 102 114 — 152 144 — — 104 113 — — 126 157 — — 91 104 105 — 126 146 124 — 131 126 — — 126 124 — 148 142 148 — — 114 131 — — 123 123 — — — 150 161 —	132 135 110 — 96 130 — — 98 134 — — 144 184 — — 144 164 — — 150 178 — 159 121 136 — — — 102 114 — 152 144 — — 104 113 — — 126 157 — — 91 104 105 — 126 146 124 — 131 126 — 129 142 148 — 128 114 131 — 128 114 131 — 128 114 131 — — 123 123 — — — 150 161 — —

TABLE 28.

Mean Diameter of the Red Blood Cells.

Venous Blood. All Infants.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
106	-	8.0	8.4	_	_	8.5
111	_		7.6	8.3	-	
120	8.0	8.0	_	8.1	8.6	
122	8.0	8.0		-	8.0	-
123	7.6	7.9	8.4	_	_	
124	8.1	8.5	-	_		-
125	7.8	8.1	_			-
129	_	_		7.9	8.1	
130	_	_	7.8		7.8	
131	7.5	7.6	-	-		
132	_	_	8.0	-	8.2	-
133	7.0	7.3			_	
134	7.3	8.1		7.9	-	
135	_	7.6	- 1	7.9	-	-
136	7.8	8.1	_			_
137	7.6	8.2	- 1	_	-	_
138	_	7.9	- 1	_	7.5	_
139	_	7.8	_	7.2	-	-
140	8.0	8.1	-	-	-	-
141	7.3	7.6	8.1	"	_	-
142	_	8.3	7.8	_	_	_
143	_	7.9	_	_	_	7.3
144	7.8	7.8	_	-	_	
145	7.4	7.8		-	-	
146	7.6	7.8	_		-	-
147	_	_	_	7.5	7.7	-
148	7.4	7.7	_		-	-
149	7.3	7.7	_	-		
150	7.4	7.8			-	
151	7.8-7.71)	7.7	_	-	-	-
152	8.0-7.91)	7.7-7.81)	-	-	-	
153	_	7.5-7.51)	7.7-7.71)		-	-
154	7.4-7.61)	7.5	_	-	_	-
155	-	7.5	7.4	-		
156	_	7.6	7.8	_	_	_

^{1) 100} and 200 cells measured c = capillary blood.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
157	7.6	8.0				
158	7.0		7.6	8.0		-
159	8.3	8.1		-		
160	7.1	6.8		****		
162	7.3	7.4	_		_	-
164	_	7.4	7.1	_		
166	7.2-7.21)	7.9-7.91)				-
168	7.0-6.91)	7.9		_	7.0-7.01)	
169		7.7	_		_ '	7.4
170	7.6-7.71)	7.7	_	_	_	-
171	7.2	7.2	7.0	_	_	
172	7.3	7.4	7.1	_	_	_
175	7.9—7.76	-	_	_		7.7
176	7.2	7.8	_		7.6	-
177	_		_	7.6	_	7.5
178	7.5-7.60	7.9-7.90	_	_	_	
179	_	7.7-7.40	7.3-7.20	_		
180	8.1	8.1	_	_	7.8	
181	7.8	7.9		_	7.9	***
183	_	_	7.5	7.3	-	
184	_	7.5—7.6	7.2	-	-	_
185	7.3	7.4				
186	7.3-7.40	7.7—7.80	_	_		
187		7.4-7.50	7.8-7.7c	_	-	
188	7.6-7.60	8.1-8.10	_	_	_	_
189	7.1	7.9	_	_		
191		8.2-8.20	8.1	_	-	-
192	_	7.9	_	8.1-8.00		-
199	8.5	8.0	_	-	-	
200	8.0	8.1	-	_	-	
201	8.1	8.1		_	_	
202	7.8	8.6		_		
203	7.8	8.4		-		-
205	-	_	7.7	8.3	-	
206	7.5	8.0	******	_	-	-
207	7.8	7.9	_	_		-
208	-	8.4	8.6	_	-	_
210	8.1	8.3	_	_	_	-
214	_	7.7	8.5			

 $^{^{1}}$) 100 and 200 cells measured c = capillary blood.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
216	7.6	7.8	_	7.9	_	
218	_	-	8.0	7.8		
219	_	7.9	7.5	_		-
220	_	- 1	7.4	7.5	****	
222	_	7.3	-	_	7.5	-
223	-	7.9	-	7.8		
224	7.2	7.3	*****	-	-	
225		7.5	7.7	7.7		
226	7.7	8.2	_	-		_
227	_	7.6	8.0			-
233	_		7.2	_	7.5	-
234		_	8.2	-	8.1	-
235	-	7.4	7.3			
236	7.7	7.7	-		7.5	-
237	7.5	7.7	7.5			
238	_	7.7	-	7.3	-	-
241	-	8.0		7.5	_	7.5
242	7.5c	7.8-7.80	-	-	_	-
243	8.3—8.5c	8.8	-	-		
245	7.8-7.70	_	_	_	_	****

1	124	8.1	8.5	- 1	1		- 1
1	134	7.3	8.1	_	7.9	-	_
1	164		7.4	7.1			
1	166	7.2	7.9	_		-	
1	171	7.2	7.2	7.0	_		_
1	172	7.3	7.4	7.1	-	_	_
1	177	****		_	7.6	_	7.5
ı	180	8.1	8.1	_	_	7.8	_
L	181	7.8	7.9	_	-	7.9	
1	183	-	_	7.5	7.3	_	
	185	7.3	7.4	_	_	_	-
1	189	7.1	7.9		_	_	_
1	191		8.2	8.1			-
	210	8.1	8.3		_		-
1	236	7.7	7.7	_	_	7.5	
	237	7.5	7.7	7.5	_		_

c = capillary blood.

TABLE 29.

Haematocrit
Venous Blood
All Infants.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
78	45	64			_	
81	59	44	_			
82	67	79	_			
83	50	63	_			
91	40	56				_
129	_	_		72-71	7371	
130	_		6464		6469	
131	5051	55—55				
132		_	67—66		6060	-
133	52-47	59—60	_			
134	65-66-66	82-84		7174		
135	_	7065		6263		_
136	58-52	59			_	-
137	58-60	60-57				
138	_	68-70	_	_	6464	
139	_	6565		66-69		*******
140	67—65	74-74			_	
141	5860	6563	6365		444	-
142	_	6868	70	_		
143	- 1	71	_			676
144	58-60	72-74	_	_		
145	5759	6867	_			-
147	_		_	5358		535
148	5656	6060	_		-	-
149	5557	62-62	_			potentia
150	6265	6566	_			addressed.
151	59—58	69—68	_		_	
152	56—56	66-66	_		_	-
153	_	72-72	75-74		_	-
154	64	68-70	_	_	_	_
155	_	6060	6465		_	-
156	_	75-74	75—78	_	_	
157	51-52	6365	_			
158	_		72-72	72-75		
159	50-50	5556	_	_		
160	53-54	74-74		_		-

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
161	52	4950	_	_	_	_
162	54	64		_	_	
165	67	66				
167	59	68	_	_	_	_
168	5961	60-60		_	56-55	
169	_	72-72		_	_	66
170	5454	56-57	_	_		
175	60-58	64-64			_	62-6:
176	5453	6666	_	_	62-62	- 0,
184	54-53	68—66	6969	_		
186	54	6060	_			
187	-	68-67	73—73			
188	61	70—70	75-75			
190	01	70-68	7272			
192		78—78	/2/2	74—76		74-76
214		62-59	5454	74-70		24-75
215		76-74	71-73	70-71		
216	6060	64-64	-/3	70-71		-
217	6263		1			
		70-70		70 71		
218	_	05 05	71—73	70-74	_	
219	-	6567	59—61		-	-
220			68-64	6565	_	1000
221	62-62	66-68		_	-	-
222	-	63—64	-		57-57	-
223		50	-	50	-	-
224	54—55	64	- 1	-	60-60	
225	_	72—73	-	76-78		
226	61-62	72-70	-		-	
227	- 1	59—57	61	-	-	
228	56	55—55	-		-	
229	54-54	6866	-			-
230	-	-	59—59	-	6161	-
231	53—54	58-58	-	-	-	-
232	6365	67	-	-	-	-
233	-	_	5555	-	56-58	-
234	_	_	78-80		78	-
235	_	73-72	72	_	_	_

Infants boru by abnormal deliveries.

Child No.	Birth	2 hours
81	59	44
1)82	67	79
1)131	51	55
159	50	56
161	52	50
1)221	62	67
1)228	56	55
1)232	64	67

TABLE 30.

Resistance of the red blood cells against hypotonic sodium chloride solution.

Total Haemolysis. Venous Blood.

Child No.	1. Er.	1. NaCl	2. Er.	2. NaCl
280	5.20	0.40	4.60	0.36
281	5.52	0.40	5.22	0.38
282	5.45	0.40	5.02	0.40
283	5.87	0.34	5.72	0.36
284	5.53	0.36	5.48	0.36
285	6.10	0.28	5.64	0.26
286	6.18	0.28	5.98	0.26
287	6.01	0.26	5.49	0.28
288	5.20	0.26	5.20	0.24
289	5.78	0.28	5.45	0.26
290	6.34	0.20	5.80	0.24
291	6.48	0.20	6.00	0.22
292	4.96	0.22	4.71	0.22

¹⁾ Caesarean sections.

TABLE 31.

White Blood Cells.

Venous Blood Capillary Blood

		Diooa		Cup	mary Bioca	
Child No.	Birth	2 hours	hours	Birth	2 hours	4 hours
48	17,100	21,800		45.500		
49	11,900			17,500	29,300	_
50	12,700	16,600	10.500	13,200	17,600	
51	14,600	16,100	19,500	13,500	17,800	21,30
52	11,900	18,900	25,700	16,500	19,200	28,90
53	1	15,300	15,100	13,700	16,600	16,50
54	13,500	13,800	_	14,300	13,700	-
55	40.000	41.000				*****
	10,300	14,800	10,900	11,700	15,200	11,500
56	9,600	15,000	11,200	10,900	15,200	11,300
57	9,100	15,100	10,200	9,300	16,100	10,800
58	12,500	12,100	13,600	12,800	12,000	14,400
59	13,900	13,000	13,200	14,500	13,700	13,600
60	20,600	20,900	21,700	21,300	24,000	22,300
61	9,300	14,200	10,500	9,600	15,100	10,700
62	_	-	-	15,500	17,100	15,300
63	14,300	18,700	15,400	15,500	20,000	15,700
	14,800	18,600	14,600	15,700	19,900	14,900
64	15,600	18,000		16,200	18,400	10,400
- 1	15,600	18,100	_	16,400	18,500	-
65	10,300	10,400	11,800	10,300	10,200	12,300
	10,200	10,400	11,900	10,500	10,400	12,300
67	14,100	15,600	15,100	13,400	15,100	14,700
	14,000	15,500	15,500	13,600	14,900	14,900
68	16,200	15,000	13,900	_	_	_
69	12,700	12,400	12,600	17,100	14,400	
	13,100	12,200	12,800	16,500	14,600	
70	13,200	16,600	13,000	_	_	
	13,700	16,400	12,900	_		
71	14,000	20,700	12,100	_		
	14,300	20,300	12,400	_		
72	10,700	11,600	12,600	11,900	14,100	12.600
	10,600	11,500	12,700	12,300	13,900	12,600
73	_	8,900	11,400	-2,000	.0,300	14,000
	_	8,800	11,400			
74	13,200	15,300	11,600			
	13,600	15,100	11,200			
75	13,100	9,500	13,200	-	-	

Child No.	Birth	2 hours	4 hours	Birth	6 hours	8 hours
	13,500		_		_	
76	15,200	17,600		-		-
77	11,200	19,200			_	-
	11,100	_				No.
78	11,600	12,600		Million.		-
79	11,000	12,100	_	******	_	
80	10,200	11,100	_			_
82	12,600	13,100	- 1	-	_	_
83	11,100	11,800		-	_	
84	8,900	8,800	- 1			*****
86	10,600	8,700	10,300	_		-
87	11,300	10,500	9,600			-
88	11,900	12,200				-
90	9,800	9,600	_	anning.		-
98	10,200	12,200	-			-
99	9,000	8,500	_		_	
100	6,400	8,400	9,500			-
102	11,400	9,400	-		_	
103	13,100	14,300				_
104	7,000	4,000	-	_	-	-
105	15,300	12,600		-	-	_
106		13,000	13,200	-		
107	13,000	14,400	-	-	-	•
118	8,500	7,900	_	_	-	
119	11,700	13,400	13,300	-	_	
120	8,400	9,000	8,900		-	_
122	9,000	9,500			****	_
123	8,900	9,500	9,300			-
134	7,900	10,500	-		Marine M.	No. of Lot
195	8,000	9,000	-			

Daily values.
Venous blood.

Child No.	4 hours	day	2 days	3 days	4 days	5 days	6 days
70	13,000	11,400	7,200	12,300	_	_	
	-	11,700	7,600	-	_	_	
71	12,300	12,500	10,100	_	8,100	7,900	
	-	12,500	10,000		8,100	7,700	
72	12,700	14,000	_	11,800	8,000	7,500	9,000
		-	_	11,900	8,400	8,000	8,70
73	11,400	10,200	9,200	8,000	8,100	9,200	_
		10,000	9,000	7,600	8,100	8,900	_
74	11,800	9,200	8,000	8,500	8,000		
		8,200	8,100	8,300	8,000		
75	13,200	9,100	8,900	8,700	_	-	-
		9,300	9,200	_		_	
76	-	10,500	10,800	9,600	_	Person	-
	-	10,100	10,700	9,500			-
86	10,300	11,900	10,800	-	_		4.000
87	9,600	9,300	9,300	9,200		-	
88	-	11,300	10,400	9,800	_		

TABLE 32.
Differential Blood Count.

98

Table 32. (Cont.)
Differential Blood Count.

		-										100
Child No.	Age	Eos	Bas	Mye- loc	mye- loc	Stab	Segm	Ly	пос	Macro- bl.	Nor- mobil.	ma- cells
	1	8.0	0.5	0.3	3.0	5.5	42.8	45.5	6.3	5:400	1:400	1
	II	-	0	0.3	8.0	8.8	55	32.3	9	3:400	1:400	1
	III	8.0	1	1	8.0	8.9	57.3	30.8	3.8	3:400	2:400	1
	I	1.8	0.3	0.3	0.5	3.3	48.3	43.5	2.3	7:400	12:400	-
	11	1.5	0.5	0.5	1	5.5	20	39	24	5:400	5:400	-
8.2	I	1	0.5	-	31	21	59	34.5	-	5:400	3:400	Barren .
	II	1.5	0.5	1	8.0	6.5	9,9	8.4.8	-	3:400	2:400	-
	1	0.5	1	0.5	1	4.5	4.5	87	0.5	2:400	2:400	1:400
	II	0.5	1	0.5	1.5	5	53.5	38	-	1:400	1	1:400
	I	1	1	-	1.5	4	48.5	43	1	-	1:400	-
	II	1	0.5	1	0.5	65	52.5	42.5	1	2:400	2:400	
	III	-	-	0.5	0.5	3.5	52	40.5	-	1:400	1	-
100	I	0.5	1	0.5	0.5	9.5	51	34.5	2.5	1	1	
	II	©1	0.5	0.5	0.5	7.5	51	36	01	2:400	3:400	
	III	1	1	1	1	9	09	33	1	1:400	-	1
888	I	21	0.5	1	1	4.5	33.5	57	2.5	1	-	1:400
	11	1.5	1	-	0.5	8.5	60.5	5.5	1	5:400	3:400	1
	I	÷I	0.5	0.5	-	5.5	1 1	4.5	21	1:500	1:500	
	11	01	0.5			6.5	100	319.5	1.5	2:500		

-	1	-	1	1	1	1	ļ	1	1		I	1	5:400	1:400	1	1	1	-	3:400	2:400	-	1	
-	2:400	2:400	1	1:400	1	1:400	1:400	3:400	3:400	4:400	1:400	i	13:400	13:400	2:400	5:400	32:400	40:400	14:400	12:400	5:400	4:400	0.200
-	2:400	3:400	1:400	4:400	2:400	1	1	2:400	3:400	3:400	2:400	1:400	4:400	3:400	1:400	3:400	12:400	8:400	1:400	I	1	1	
1	23	0.5	00	1	1	2.2	2	1	-	2.5	10	2.2	10	3.5	21	00	9.7	9.4	8.4	6.3	4.3	2.5	3
39.5	31	52.5	43.5	26	53	32.5	45.5	29	51.5	2.4	34.5	32	20.3	26.8	46.5	30	1.1	34	38.5	31.8	17	19.5	2 20
220	59	4.1	24	39	40.5	60.5	45	59	39.5	55	55.5	56.5	26	62.5	42	57	41.3	53,3	47.5	54.5	71.8	70.5	6.0
5.5	9	4	6.5	61	4	3.5	6.5	7.5	4.5	6.5	6.5	9	8.8	3.8	7.5	7.5	10	4.3	4	2.5	4.3	4.5	e c
0.5		1	0.5	1	0.5	0.5	1	981	1	1	0.5	1	8.0	0.5	1	1	0.3	1	0.5	0.5	0.3	0.5	
-	-	1	1	i	-	1	0.5	0.5	1	1	!	1	0.3	1	1	1	1	1	0.3	1	1	0.5	M
0.5		1	1	1	1	1	-	0.5	-	-	0.5	0.5	0.5	0.5	1	1.0	1	1	0.3	-	1.5	0.5	
1	-	-	1.5	1	-	0.5	0.5	1.5	2.5	1	1.5	2.5	2.3	1.5	21	1.5	2.7	3.6	3.8	m	1	1.5	
1	II	I	II	I	II	III	I	II	I	11	П	II	11	III	I	11	I	11	III	1	II	II	TIT
86																	120			122		23	

TABLE 33.

Plasma Nitrogen (mg %)

Venous Blood.

Child No.	Birth	2 hours	4 hours	6 hours	8 hours	10 hours
87	739	1070	_	_	_	
92	1061	1142	_	_	_	
93	588	862	_		_	_
94	952	1032	_	-	_	_
95	942	1092	_	_	-	-
96	574	1120		_	-	-
98	588	624	_	_	-	_
99	590	532	_	_	_	-
100	800	880	881	_		-
102	1100	1193	_	_	_	_
130	_	_	1226	_	1027	-
131	1025-1025	1019	_		_	_
133	1130-1134	1064-1080			-	-
136	1072	958		_	_	
140	1215	1176	_	_	-	_
141	1167-1173	1187-1187	1114-1162	_		_
143	_	1064	_	_	-	924
145	1109	1086	_	_	_	-
146	1033	1092	_	_	_	-
147	_	_	_	988-988		988-98
148	1232	1148	_	_		
215	_	1234	1244	_		_
216	705	1092		_		-
220		_	1148	1198		-
221	1120	1234	_	-	-	-
222	_	1069	_	_	1055	_
223		1044-1047	_	1022-1000	-	-
224	1044	1067	etiren.	_	-	-
227	_	1167	1056		_	_
231	1064	1064	_		-	_
232	952	1075				

TABLE 34.

Plasma Protein (%).

Child No.	Birth %	2 hours	4 hours	6 hours	8 hours	10 hours					
151	6.9	7.6	_	-	_	_					
157	7.0	6.5	-	-	_	_					
159	7.6	8.1	- 1		_	-					
161	5.6	5.4	_	_	-	-					
164		6.1	5.0		_						
171	5.0	6.5	6.7								
173	8.0	9.1			_	_					
174	5.9	5.9	_	-		-					
180	7.4	8.5			_	-					
181	7.8	7.4	_			Annales.					
237	5.9	5.9	5.9	_							

TABLE 35.

Weight of the Infants.

Child No.	Birth	2 hours	4 hours
1	3,090	3,060	3.040
2	2,950	2,970	2,970
3	3,450	3,450	3,450
4	3,900	3,890	3,910
5	3,310	3,320	3,320
6	3,450	3,450	3,440
7	3,350	3,330	3,440
8	3,660	3,630	3,620
9	3,080	3,040	3,030
10	3,200	3,160	3,160
11	3,560	3,540	3,530
12	3,200	3,190	3,180
13	4,300	4,270	4,260
14	3,350	3,330	3,330
15	2,790	2,780	2,780
16	2,550	2,540	2,540
17	4,070	4,060	4,060
18	4,220	4,210	4,210
19	3,200	3,180	3,190
20	3,770	3,760	3,760

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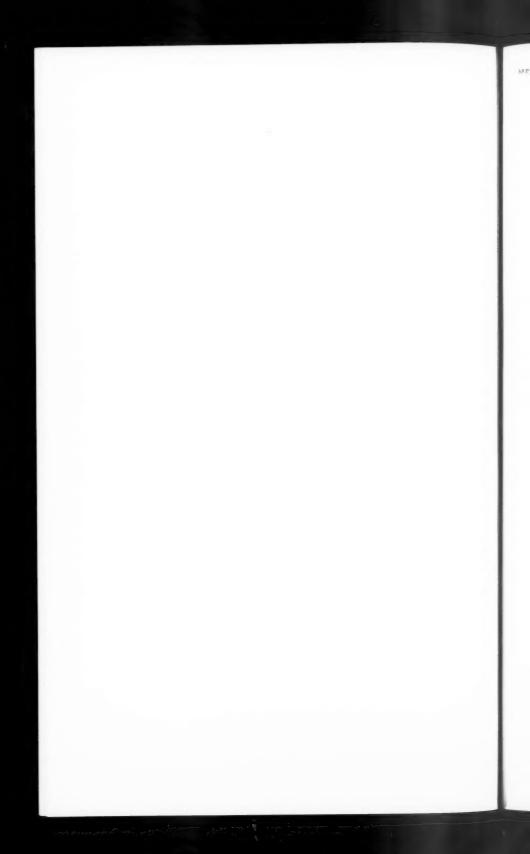
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ACTA PÆDIATRICA





FROM THE PÆDIATRIC CLINIC OF THE ROYAL CAROLINE MEDICAL INSTITUTE, NORRTULL HOSPITAL. HEAD: PROFESSOR ARVID WALLGREN

COW'S MILK IDIOSYNCRASY IN INFANTS

BY

STEPHAN VENDEL

ACTA PÆDIATRICA, VOL. XXXV, SUPPLEMENTUM V

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Introduction

The classification of idiosyncrasy to cow's milk as a clinical syndrome distinct from other digestive disturbances dates from reports published by Schlossmann and Moro (1903—05). Since then a number of subsequent publications have confirmed the existence of this disease. Its allergic ætiology may be considered as established in 1910 following investigations by HUTINEL, WERNSTEDT and others.

There has been occasional mention of the syndrome in the Scandinavian publications of the last 40 years. These remarks have been so scanty, however, that its occurrence — at any rate in severe clinical form — may still be regarded as comparatively rare.

When Povl Hertz demonstrated his patient, in 1914, only a few cases had been reported, and — with the exception of Wernstedt's 1 case — these all came from clinics in Germany. After that there was no mention of the syndrome in *Ugeskrift for Laeger*, the Danish journal, until 1947. When Rothe-Meyer reported 2 cases of his own at a meeting of the Danish Paediatric Association in 1943, Oluf Andersen pointed out that it was strange for 5 cases of such an uncommon disease to occur in Copenhagen in the space of only a few months. Nevertheless, it was a similar example of the law of coincidence which gave rise to this investigation. Of the 7 cases requiring hospital treatment which occurred in Stockholm throughout 1946, 3 were admitted to Norrtull Hospital in the course of 2—3 months. These 7 cases represent 30 per cent of all cases (23) admitted to the children's hospitals of Stockholm between 1919 and 1947.

Wernstedt (1910) was the first to describe a case of idiosyncrasy to cow's milk in Sweden. In 1918 Anna Helmer and I. Jundell demonstrated another case for the Paediatric Section of the Swedish Medical Association. Seven years later C. Gyllenswärd reported 3 cases from the Sachs' Children's Hospital, Stockholm.

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In order to throw light on the occurrence of established cases of idiosyncrasy to cow's milk over an extensive period, we have gone over the journals of the 4 children's hospitals in Stockholm¹, with the following results:

Sachs' Children's Hospital: 1914—46, 5 cases in all (1923: 3 cases; 1931: 1 case; 1946: 1 case)

Samariten Children's Hospital: 1934—46, 4 cases in all (1941; 2 cases; 1946: 2 cases)

Crown Princess Lovisa Hospital: 1915—47, 5 cases in all (1934, 1941, 1944, 1946, 1947)

Norrtull Hospital: 1919-47, 9 cases in all.

The distribution of cases at the last-named hospital is somewhat more even: one case each in 1920, 1924, 1929, 1934, then 1 in 1943, 1 in 1945 and 3 in 1946. The last 4 cases were under treatment within a 9-month period — the same number as reported by Gert von Sydow for a 15-year period at the Gothenburg Children's Hospital.

With such small total numbers as those shown here, it does not lie outside the bounds of statistical probability for examples of such an uncommon disease to appear grouped. Altogether we have a total of 23 cases in which the clinical picture and reactions are typical of cow's milk idiosynerasy. For the period 1920—46, the frequency in relation to the total number of infants born alive in Stockholm (23 cases out of 199729 births) is 1:8684 (with figures from Samariten lacking up to 1934). If we take the figures from 1934 and the figures for the last 10 years only, the ratios are 16:121292 and 14:104585 respectively, constituting in either case approximately 1 per 7500 infants. Taking the

¹ The author wishes to express his gratitude to the head physicians of the Crown Princess Lovisa Hospital and the Samariten and the Sachs' Children's Hospitals: Professors Lichtenstein and Malmberg and Docent Magnusson, for the readiness with which they placed records of their cases of cow's milk idiosyncrasy at his disposal.

numbers of cases of all kinds admitted to Norrtull and the Crown Princess Lovisa Children's Hospitals (as well as Samariten), we have in each instance approx. 1 case per 3 000 patients (Norrtull: 1919—46, 9 cases per 26 300 admissions; Crown Princess Lovisa, 1934—47, 5 cases out of rather more than 15 200; Samariten: 4 cases out of 13 400).

Another point, however, is that the number of admissions can hardly be employed as a basis of measurement of the actual frequency of this form of allergy. It gives an indication only of the frequency of occurrence of forms so pronounced clinically that the symptoms become threateningly dramatic. Actually all degrees will be found in the clinic, from unobserved or slight and misinterpreted distress after meals — moderate dyspeptic symptoms (slight oppression or distension, constipation or rather loose motions) - to cases in which even minimum quantities of cow's milk bring on a condition of shock. The infant may collapse, losing consciousness, and in exceptional cases death takes place during the attack. The numerous other allergic manifestations which may accompany the gastro-intestinal reactions have often been described and vary from case to case. Some infants contract urticaria, others only asthma etc. The extreme cases practically always come in to the hospitals, whereas the greater part of the milk allergy cases of moderate severity would seem seldom to get farther than the consulting room of the private practitioner.1 The main interest is concentrated on those few cases accompanied by shock and collapse, in which there is consequently direct danger of death each time the child is again exposed to the allergen. The essential problem is to recognize the aetiology of this alarming condition, so that risk of fresh attack may be removed by »desensitivization» or by exclusion milk from the diet.

There is a slight predominance of males over females (13: 10)

¹ Professor Nils Malmberg has been good enough to give particulars of 3 of his 4 cases in private practice in the last decade. The presence of so many cases of this anomaly in one private practice, not treated in hospital, supports the estimate of frequency presented above. 1 of Prof. Malmberg's cases (No. XXIV) is included in the table.

in the series of this investigation, but in view of the small body of material the difference is of no great significance. Moreover, owing to the variation in examinations and therapy, with the material covering such a long period and derived from different hospitals, I am not justified in drawing any definite conclusions on these points. Nevertheless, it would be extremely desirable for a series of cases of this affection, after unified and thorough tests, to be made the subjects of the simple desensitivization procedure which, rightly or wrongly, we consider responsible for the cure of the 3 last cases at Norrtull (Nos. VII, VIII, IX). Nevertheless, in view of the later prognosis of the infants in allergic respect, the material does appear to allow of certain conclusions, or at least provide a distinct pointer.

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The anamnesis is practically always so typical that the diagnosis seems obvious, though as an adjuvant an attempt at exposure may be made, possibly accompanied by determination of the leucopenic index, sensitivity determined by cutaneous or intracutaneous tests or by passive transfer test ad modum Prausnitz-Küstner (or as modified by Walzer).

The question of the reliability of cutaneous tests in clinically manifested allergic conditions has also been discussed in this connection, and the general experience seems to be that the outcome of a cutaneous test as isolated information is of but small value in judging a case, despite the unquestionably specific nature of the test itself. Particularly in food allergies as a whole, not least when in the form discussed in this paper (Hill, Randolph, Urbach & Gottlieb) cutaneous tests are not perfectly reliable; they turn out negative despite definite clinical hypersensitivity. The conditions under which agreement between test result and clinical findings may be anticipated and those under which the tests are likely to "fail", are, on the other hand, but little spoken of, though Schick & Peshkin, after stating that the allergic reaction need not necessarily follow immediately but may set in after 2 to 24 hours, write in Brenneman's that

othe sooner allergic symptoms follow the ingestion of food the greater the likelihood of obtaining a positive cutaneous reaction, while allergic symptoms occurring some hours later are usually associated with negative cutaneous reactions». No explanation is given of the delayed occurrence of the clinical reaction or of its relation to the skin test's increased unreliability.

On the other hand, it is possible to demonstrate by the skin tests that a positive reaction to cow's milk is present in a far greater number of infants than the few in whom a clinically manifest alimentary (gastro-intestinal) allergy is obtained. cutaneous tests are particularly frequent in eczema infants. HILL obtained positive reactions to the »scratch test» with milk in 17 per cent of 153 infants suffering from eczema of all types. both allergic and non-allergic. On 64 of those reacting negatively the test was repeated intracutaneously and 56 per cent then reacted positively. Since normal infants do not react positively - even after having drunk milk daily for a considerable period - Hill considers that these results furnish evidence of the aetiological rôle of milk in infantile eczema, and he finds further support for his opinion in the observation that as a rule eczema in such children disappears when they are put on a milkless diet. He characterizes milk as »by far the most important allergen in early life», not least where eczema is concerned, and he advances the opinion that eczema is the reaction of the organism against a prolonged continuous exposure to the milk allergen in small doses, whereas a sudden exposure to milk in large doses after a period entirely without it might bring out the acute general reactions which we designate as the typical cow's milk idiosyncrasy. The simultaneous occurrence of eczema and cow's milk idiosyncrasy is more difficult to explain on the basis of this hypothesis.

Cutaneous and intracutaneous tests demonstrate only the specific sensitivity of the skin, whereas the object of testing is as a rule to demonstrate the hypersensitivity of the organism as a whole. Herein lies the real limitation of all tests. They assume that the organism is allergized throughout, or in any case as regards the part taken as the object of the test. This may well happen, and then there is full agreement between the clinical and

the test findings. But in numerous cases it would seem as though only some of the body's tissues or organ systems were appreciably sensitivized, and then if the tests do not encounter one of these »shock organs» or »shock tissues», no positive reaction is obtained. It is therefore the rule that as far as possible the test should be made on that part of the organism where the clinical reaction to the allergen develops. The same conditions apply to mucous membrane tests as to cutaneous examinations. Prausnitz-Küstner's reaction and Urbach-Königstein's experiment establish only the presence of specific antibodies in the circulating plasma or the intercellular fluid, respectively, but by themselves nothing else.

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Different Clinical Types of Cow's Milk Idiosyncrasy

In many cases the first symptoms of cow's milk intolerance arise in conjunction with the first known exposure to this food, but in other cases not until the second or an even later exposure. Thus it is not unusual for an infant who has tolerated milk for a period and then not been exposed to it for some time to react violently the first time it again encounters the allergen. The distinction formerly made between sidiosyncrasys and sanaphylaxiss seems no longer to be maintained; it is now presumed that the mechanism is the same in principle.

Nevertheless, von Sydow, who began on this basis to classify 4 cases of his own and 12 others from the literature, arrives at the conclusion that a distinction may be made between 2 clinical types. In the one there is an obvious constitutional basis for hypersensitivity, in that the infant reacts to cow's milk with symptoms of the skin or the respiratory tract also and is not so susceptible to desensitization therapy. The other type, however, is less markedly constitutional in origin; the infant displays symptoms of the digestive organs only and fairly quickly acquires tolerance of cow's milk. Here it is a question of cases which develop allergy only some time after the primary exposure.

The cases described in this paper will be classified on quite another basis, though it will be demonstrated that we still come

to the conclusion that there do exist 2 such distinct clinical types as von Sydow claims. The mere fact that in certain cases only the digestive canal and in others still other systems of organs are concerned in the allergic attacks will not constitute the basis of our classification. This circumstance might well signify merely a difference in degree of reaction ability and thus be a purely descriptive classification, without grounds in any profound difference between the types presented. Nevertheless, as regards prognostic it might have importance in itself, since conditions might be such that the more of the organism's tissues that were affected by the sensitivity - or the greater number of regions which could be designated »shock tissues» or »shock organs», in Urbach's terminology — the more dangerous exposure to the allergen would be to the continued existence of this organism. - No cases of melæna allerg, infant (Rubin) are included.

Case Reports

We now give brief case reports and comments on the 23 cases.

Case I. Norrtull Hospital (NH) 39/1920. Female infant without any known allergic predisposition. Weaning tried in third week. After 2 meals of cow's milk the child reacted with violent vomiting fits, with a 2 hour free interval. A third attempt was made at the age of 4 \(^1/2\) months. 2 hours' latency, then vomiting lasting for 2 hours; normal temperature after 3 days. Diarrhoea for 4 days, with defaecation every second hour during the first days. At the age of 8 months the child was subjected to a new trial. She reluctantly accepted 5—6 teaspoonfuls of diluted milk, vomited after 2 hours, had 3—4 loose stools. — When, after 2 months, she was again given 20 cc diluted milk, she wailed the entire night and had 3 loose stools, but no vomiting. On the two latter occasions afebrile. — Admitted to the hospital at the age of 10 months, stayed for a month. No special desensitization performed. The child was placed on a milk-free diet until, after the lapse of 24 days, a daily addition of 35 grammes of cow's milk was well sustained.

Comments: Attacks at ages of 3 weeks, $4^{1}/_{2}$, 8 and 10 months respectively. Latency 2, 2, 2 and ? hours. No known inherited predisposition. By the age of 11 months spontaneous tolerance had developed. Irrespective of milk, digestion remained troublesome up to the age of 7 years. Every second week the patient developed a temperature and had vomiting and diarrhoea of two days' duration. At 7 years a non-tuberculous pleurisy.

Case II. NH 668/1924. Male infant, the fifth child in the family. Father afflicted with severe asthma. Infant breast-fed for 3 weeks, then bottle-fed. Unsuitably nursed. Early tendency to catarrhal infections. Admitted 14/7 in bad general condition following 24 hours of high fever. Given mother's milk only. Now and then a small addition of cow's milk tried. Vomited each time. — 12/8: $2^{1}/_{2}$ hours after being fed with 200 cc milk-mixture the child reacted with a violent fit of vomiting, cyanosis and seediness. Improvement after 2 hours. 21/8: some repeated. — 4/9: violent fits of vomiting $2^{1}/_{2}$ and 4 hours after case in, (as a salt of sodium) 1 gramme. — 5/9: after whey no vomiting, but 32/9 and 23/9 several violent fits of vomiting after 4 and 8 grammes respectively of case in. — 30/9-5/10 a daily 200 cc of 2/3-milk tolerated. — 11/10: after 6+6 grammes of case in vomited altogether 190 grammes. — 13/10 the same exactly repeated.

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Comments: Attacks at ages of 3 $^{1}/_{2}$, 4, 4 $^{1}/_{2}$, 5, 5 $^{1}/_{2}$ and over 6 months with latencies of —, 2 $^{1}/_{2}$, 2 $^{1}/_{2}$ —4, —, — hours. In this instance the casein was found to be the allergen. The child's later allergic history unknown.

Case III. NH 301/1929. Female infant. At 6 weeks had her first meal of cow's milk, viz. 150 cc of $^1/_2$ -milk, reacting with bad colour, fits of vomiting, diarrhea and loss of weight. When 2 weeks later the exposure was repeated, the same reaction occurred. The child was then immediately admitted. From the second day of her stay at the hospital she tolerated $^1/_2$ -milk¹, beginning with 150×1 . In 12 days no trouble with 180×3 .

Comments: Attacks occurred following exposure at ages of 6 and 8 weeks. Data regarding latency and heredity lacking. Without any special measures she became tolerant soon after admission to the hospital. In later life no other allergies have appeared. (This case not included in the table.)

Case IV. NH 610/1934. Male infant. Breast-fed, without any allergic predisposition. As early as his first week tolerated 10 cc of cow's milk as an addition to each meal. Was then given no cow's milk until the age of 4 months, when, at the 6 p. m. meal, 50 cc of ¹/₂-milk was added. After 4 hours the child became motionless, greenish-pale, had a violent fit of vomiting and looked lifeless for a whole hour. Then had an uneasy night, now and then wailing a little. In the morning a tempera-

 $^{^1}$ $_{^9}1/_{^9}$ -milk» consists of equal parts of cow's milk and a decoction of outmeal sweetened with 5 % sugar and approximately $^1/_2$ % sugar. The concentration of the oatmeal decoction is approximately 1 %: 1 dessert spoon (= 5 g) of cereal to $^1/_2$ litre of water. $_{^9}2/_3$ -milk» = $1^1/_2$ dessert spoons of cereal for decoction, which is mixed with 66 % milk.

ture of 38.5° C. Had 3 malodorous diarrhoea stools. — At the age of 5 months the same shock condition recurred 3 ½—4 hours after the infant had been given 2 tablespoons of cow's milk, though he was not quite so much affected as before. Admitted to the hospital a month later; stayed 2/10—12/10. Two hours after being given 15 cc of cow's milk the child reacted with paleness, repeated fits of vomiting, loose defaccation. Sick for ½ hour. Two days later, 2 ¼ hours after 5 grammes of cow's milk, a slight fit of vomiting but general condition unaffected. During the following week a daily dose of cow's milk was administered and progressively increased from 10 to 100 cc without any particular discomfort or obvious effect on the leucopenic index.

('omments: First tolerated milk for a period. Then 4 attacks at ages of 4, 5, 6 and 6 months with latencies of 4, 3 1/2-4, 2 and 2 1/2 hours respectively. During the following weeks the infant grew accustomed to progressively increased quantities of milk. No reaction. Later in childhood he has always tolerated milk and never displayed any other allergic reaction. Strangely enough, this child reacted to 30-50 cc of milk with far longer latencies than when exposed to milk in small quantities, viz. 5-15 cc per dose. Probably no reasonable explanation of this circumstance can be advanced until the actual cause of latency periods has been generally explained. A tempting hypothesis would be that the milk primarily provokes a spasm in the pylorus which in some children passes off in a few minutes, in others only after a lapse of 2 to 3 or 4 hours. After that the way to resorption would be cleared and the shock mechanism become active. But such a tentative explanation, naturally entirely hypothetical, does not provide any answer to the question of why the cutaneous reactions become negative when there is a long period of latency.

Case V. NH 1055/1943. Female infant with slight allergic heredity. At the age of 1 week had a brief period of diarrhoea. Then an addition of 5 cc ordinary cow's milk to each meal did not trouble her. The next exposure occurred when at the age of 5 months she had her first meal of \(^{1}/_{2}\)-milk-soup and immediately developed a fit of vomiting. Is said not to tolerate butter either. Poor increase in weight in the month preceding her admission when on diet of tea, fruit-juice soup, pap and only 500 grammes of mother's milk. For this reason, 1 teaspoonful of unboiled cow's milk was tried a week or so before admission. This was followed 2 hours later by fits of vomiting. — On another previous occasion the child was unconscious for 1—2 hours after having consumed 10 cc cow's milk. Admitted at the age of 6 \(^{1}/_{2}\) months for 8 days, \(18/8-26/8\). Rhagades at right ear, otherwise w. c. Percutaneous test not definitely positive, either with cow's milk or eggalbumen. On 24/8, a small dose of cow's milk (1—2—3—4 and, finally,

5 drops) administered every second hour without any reaction. Afterwards the girl was easier to feed than before. 25/8: Intracutaneous test with the same substances without any definite positive reaction. The erythema from cow's milk was, however, twice the size of that of the control but soon faded away at the same rate as the control. — Subsequently 50 grammes of unboiled cow's milk was administered without any vomiting or other allergic reaction. Differential count disclosed only 1 per cent eosinophils (26/8). The anamnesis revealed a definite idiosyncrasy to cow's milk, but tests per os or cutaneously failed to produce any objective signs of hypersensitiveness.

Comments: Attacks at ages of 5, about 5 $^{1}/_{2}$ and 6 months, with latencies of —, 2 and 2 hours respectively. Scratch test faintly positive, but just before the intracutaneous test, which proved negative, a small quantity of milk was administered as in a *desensitization experiments on a small scale, and the tolerance to milk in progressively greater quantities improved rapidly. Nevertheless, during the following 3 months mother's milk alone was given. At 9 months the girl was weaned and for about a week showed intolerance to cow's milk. During the later part of her first year she had a mild eczema which by the end of the year was but slightly in evidence. In later childhood no asthma or other allergic manifestations.

Case VI. NH 678/1945. Male infant, breast-fed, with some allergic predisposition. On several occasions before admission reacted to cow's milk. At the age of 2 \(^1/_2\) months had a meal of \(^1/_2\)-milk, 150 grammes. 2 hours later turned pale, grew weak, vomited, had diarrhoea and did not fully recover for 24 hours. 2 weeks later the same reaction to 2 teaspoonfuls of boiled cow's milk. The same latency. On later occasions the same results obtained after a few spoonfuls of boiled cow's milk and also after citric-acid milk. At the age of 5 months admitted for 3—4 weeks. Cutaneous tests then proved negative, both before and after the desensitization trial, which was performed with increasing quantities of cow's milk and a gradually shortened boiling time.

Comments: Attacks at $2^{1}/_{2}$, 3, about 5 and $5^{1}/_{2}$ months, always with a latency of 2 hours. After administration of boiled milk according to schedule the child acquired tolerance. However, both before and after desensitization the cutaneous tests remained negative. Unfortunately the Prausnitz-Küstner reaction was not applied. At 1 year the child was hypersensitive to ordinary fruit and some time later to eggs. At $1^{1}/_{2}$ years had an extensive food rash, the actual cause being unknown. Neither eczema nor asthma have occurred. During the past 2 years milk has been well tolerated.

CASE VII. NH 278/1946. A boy, 4 months old, only child. The father had had asthma. During his first week at the Maternity Hospital

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the child was slightly asphyctic, maintaining his body temperature only with difficulty. He was breast-fed without addition of other food until the age of a month. Then the mother thought she had too little milk and as an experiment a small addition of cow's milk was given for 3 days. This immediately resulted in vomiting and diarrhoea every time the addition was given. Then for some days the child had mother's milk only and no vomiting or diarrhea occurred. The mother again tried an addition of cow's milk. The same reaction, vomiting and diarrhoea, as before. Once more the child was fed with mother's milk only. This went on until he was 4 months old, i.e. shortly before his admission. He had then had eczema on his cheeks for a month. The result of administration of milk was violent fits of vomiting, erythema over the entire body and a general condition verging on collapse. At the time of arrival he was in a state of shock, pale, with urticarial hives on the body and eczema on the legs. Cutaneous test with cow's milk proved negative. Intradermal test of 10 per cent solution of cow's milk gave a positive result and, in addition, a severe general reaction with an extensive urticarial erythema, necessitating adrenalin injection and administration of stimulants. Passive administration according to Prausnitz-Küstner (in Walzer's modification) gave positive result. Peroral administration of 60 grammes of cow's milk produced a violent general reaction and erythema, the number of white corpuscles falling by 20 per cent (polynuclears 33 per cent). With a diet free from cow's milk the eczema disappeared. After about a week strongly diluted and well boiled milk was administered, to begin with in exceedingly small amounts, then in larger doses less diluted and less boiled. When he was discharged after 3 weeks the skin of the patient looked normal and he tolerated addition of the necessary quantity of diluted cow's milk. Prausnitz-Küstner's reaction was now negative. At a new determination of the leucopenic index no definite reduction in the number of leucocytes was demonstrable. Nor did the 60 cc of cow's milk administered provoke any general reaction. Since then he has tolerated cow's milk even during periods of illness. 2 months after his discharge he fell ill with otitis and was admitted to the hospital for a few days.

Comments: Attacks at the age of 4 and 5 weeks and 4 months. On the first occasion he reacted simmediatelys, then after 1 hour and when the cutaneous tests were made after $1^{1}/_{2}$ or 2 hours. Up to the age of 13 months he reacted to milk with pains in the stomach. For a transitory period he could not tolerate eggs or tomatoes. Subsequently he has reacted to eggs, orange juice, lemons, grapes, chocolates, nuts and shellfish with abdominal pain.

Case VIII. NH 482/1946. This case concerns a boy 6 months old. His father had eczema as a child and was later troubled with asthma up

to his fifteenth year. The boy had been exclusively breast-fed. When I month old he had eczema on the face. When at 5 months cow's milk was tried he at once had fits of vomiting and diarrhoea. 3 weeks later the experiment was repeated with identical results, viz. vomining after a few minutes and a strongly affected general condition. After 45 minutes he was free from symptoms. He was then admitted to the Clinic. Extensive, strongly itching, partly weeping, eczematous challens, principally in the face. Eosinophilia 30 per cent. Cutaneous test markedly positive to egg-albumen; less pronounced though definitely positive reaction to cow's milk. Intracutaneous test of 10 per cent unbested cow's milk produced an extremely powerful reaction, less pronounced to milk boiled for 12 minutes. Prausnitz-Küstner's reaction positive to egg as well as to cow's milk. The boy was subjected to ordinary local treatment for the eczema and a diet excluding cow's milk. The eczema rapidly improved. Then desensitization according to the previously defined schedule (comprising 11 days) was tried without any signs of general or cutaneous reaction. Discharged after 3 weeks with normal skin. He then tolerated only a small amount of 1/g-mill but gradually increasing quantities at home up to 150 grammes were prescribed.

Comments: The attacks occurred at 5 and less than 6 weeks of age, both times only a few minutes after exposure. For a year after his discharge from the hospital he always tolerated milk well. However, the eczema periodically reappeared, particularly after the boy had eaten food of the kind found by experience usually to provoke strophulus in him, viz. eggs, chocolates, oranges, bananas, spinach, fish and to some extent meat, according to the mother's statement. When suffering from colds he has also shown mild symptoms of asthma several times since his return home.

CASE IX. NH 410/1946. This last case concerns a boy 8 months old whose father had eczema as an infant and remained sensitive even as an adult, reacting to various foods in different ways.

At the age of 2 months the boy had eczema of a weeping type combined with severe itching, first in the anal region, then also in the face. Administration of orange juice aggravated the eruption and was discontinued by the mother. At the age of 4 months he was admitted to the Clinic because of the eczema, which then was spread over the face and extremities, partly weeping, partly lichenous, and accompanied by severe itching. Cutaneous test with egg-albumen positive, with cow's milk negative. Eosinophilia 19 per cent. He was fed with mother's milk exclusively, treated for his eczema, which rapidly improved, and discharged after a fortnight.

After return home the eczema again took an unfavourable turn,

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girl 8 exud but all the same his condition was not too bad until, by way of experiment, the mother gave the boy, then 8 months of age, 2 tablespoonfuls of cow's milk. He then had extensive urticarial hives, particularly in the face and parts that had come into direct contact with spilled milk. The hives appeared within less than a minute and vanished after an hour or so. The eczema became worse. No digestive symptoms, no shock effect. Again the child was given only mother's milk and became free from symptoms. After 3 weeks the mother gave him a weaning meal of 150 grammes of 1/2-milk, resulting in hives in the face, edema in hands and feet and a general erythema with severe itching. On this occasion no digestive symptoms nor shock effect. After a few days the same addition of cow's milk was tried with the same resultant symptoms. Once again the child was admitted to the hospital. As when previously treated at the Clinic, percutaneous test of egg-albumen was positive. This time, however, an additional cutaneous test of cow's milk was made. Any small drop falling on intact skin would cause redness and papulation within 5 minutes. After peroral administration of 20 cc cow's milk the leucopenic index was taken. The number of white corpuscles fell from 16 000 to 12 150, i. e. a total reduction of 24 per cent. The polynuclear white corpuscles showed a 29 per cent decrease. No general reaction noticed. Prausnitz-Küstner's reaction (in Walzer's modification) negative. The boy was desensitized in the same manner (11 days) as the previous patient. After 2 weeks discharged without any trace of skin affection. He then tolerated 75 grammes 1/2-milk without any reaction. Follow-up examination, a month or so later, showed that his sensitiveness to cow's milk was still eliminated.

Comments: Attacks at 8, 8 ½ and less than 9 months, with a couple of minutes latency. In this instance the allergy seemed to be exclusively cutaneous, though reactive not only to direct contact with milk but also to resorbed allergen. No particularly conspicuous general reactions of any kind occurred. The case was almost solely a matter of cutaneous allergy to bovine milk. The skin as a whole could be regarded as shock tissue». This was obvious from the diffuse redness over the entire body with a simultaneous digital edema which occasionally accompanied the local reactions. Case XXIII shows a similar isolated contact allergy of the skin. When at home after his hospital stay the boy tolerated milk without the least inconvenience but when tasting gooseberries, whortleberries or spices, a red rash would at once appear around the mouth. He shows no signs at all of eczema or asthma. Apart from an occasional nasal catarrh he is completely healthy in every respect.

Case X. Crown Princess Lovisa Hospital (CPLH) 336/1934. A girl 8 months old admitted on diagnosis of idiosyncrasy to cow's milk + exudate diathesis. In the hospital from 29/4 to 16/6 1934. Both parents

²⁻⁴⁸⁵⁴⁷ Stephan Vendel

healthy. A maternal uncle has asthma; otherwise there are no aller. gic affections in the family. Since the age of 1 1/2 months the girl bas had eczema, first localized to the cheeks and round the scalp, then gradually extending to the body and extremities. The red parts of the skin are partly dry and crusted, partly weeping and papulous. 3 months ago the first symptoms of alimentary hypersensitiveness appeared. The first time she tasted cow's milk (in the form of 1/2-milk) she fainted. After a quarter of an hour she was strongly affected and for a short while turned pale and became slack but had no spasms. She had a palpebral edoma lasting for 24 hours. Apart from mother's milk she had been given only orange juice. One week later she was given vegetables also. 2 me. hs later she had a new sfainting fits without any connection with make Several times during her stay at Ljungby Infirmary she had a landal edema after taking cow's milk. Following her admission to this hours. tal the same reaction was noticed and in addition, after varying intervals, vomiting fits, coughing and asthmatic attacks. Goat's milk also caused coughing fits. Cutaneous tests were not performed but the clinical picture was convincing enough.

Comments: The first attack, at 5 months of age, came 15 minutes after contact with the milk. The latency for later attacks has not been stated but seems to have fallen rather below this interval. Like case XX and the first of von Sydow's 4 cases, she was hypersensitive to goat's milk as well. She was not subjected to cutaneous test nor to desensitization. For a whole year she continued to react to milk with fits of vomiting and labial and palpebral edemas. The eczema remained troublesome up to 16 months, after which it gradually improved. During this period she was admitted to Flensburg's Children's Hospital at Malmö (case history number: 180/1934), where she was treated for 7 months under the diagnoses of idiosyncrasy to cow's milk and exudative diathesis. When discharged she was still not 17 months old. At this time the eczema was extremely persistent. Periodically she had asthma, provoked not only by colds but also by cow's milk per os. This ceased entirely after her second year, but up to the age of 6 years she was a nervous child with restless sleep. On one occasion during her sixth year an ugly nettle rash broke out on the front of the body, the cause being not quite clear. The efflorescences were the size of »small saucers». No relapses have occurred. However, 1/2-1 year ago a transitory edema appeared around the eyes on two occasions without any ascertainable cause. A younger brother has a mild eczema and another brother asthma.

CASE XI. CPLH 720/1941. Boy with exudative diathesis admitted when 10 months old. Diagnosis: idiosyncrasy to cow's milk? From the age of 2 ½ months he had an eczema of usual type and localization. For the past few months the eczema has been almost cured. The only allergic individual in the family is said to be the paternal grand-

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mother, who as an infant had a similar eczema. Between his twelfth and twenty-fourth days of life the boy was treated for mild dyspepsia, with addition first of casein Na, later citric-acid milk 20 grammes × 5 daily. Otherwise he had nothing but mother's milk up to the age of 6 months, when a small addition of 20-30 grammes wheatmeal soup was tried. The boy vomited immediately afterwards upon this and several later occasions when trials were Nor has he tolerated baked custard, which gives him vomiting fits and diarrhoea. For the past 6 weeks he has been given fruit sauce and semolina porridge to which more milk has gradually been added (during the last weeks 75 grammes of milk and 75 grammes of water). This has been well tolerated. - During his stay at the hospital the cutaneous tests (P. D. & Co.) gave positive reaction to cow's milk and eggs. Blood eosinophilia amounted to maximum 13 1/2 per cent. When larger doses of cow's milk were added, urticarial efflorescences would occasionally appear on the neck. The case was considered an extremely moderate idiosyncrasy to cow's milk.

Comments: On several occasions between the ages of 6 and 8 $^{1}/_{2}$ months the boy reacted immediately to cow's milk in spite of the fact that in his first month he tolerated milk well. By gradually getting accustomed to milk he conquered his idiosyncrasy. Nevertheless cutaneous sensitivity remained for the time being. For the next few years he tolerated only small quantities of milk. Larger doses provoked asthmatic attacks. — Cutaneous tests at the age of 4 years showed that eggs, house dust and wool as well as milk produced a positive reaction. Any of these 4 substances may bring on his asthma. He is particularly sensitive to eggs. After a few minutes he feels sick, has diarrhoea and fits of asthma. In his mother's family an allergy to eggs is common. — A younger sister gets a skin eruption resembling eczema after eating eggs. — The patient's persistent eczema continued to the end of his first year, being principally localized to face, neck and extremities.

Case XII. CPLH 370/1944. Boy with a typical anamnesis and hypersensitiveness to cow's milk of remarkably long duration.

At 2 months of age he tasted cow's milk for the first time (1 teaspoonful of $^1/_2$ -milk gruel). 5 hours later a typical attack occurred, beginning with coughing and followed by violent fits of vomiting and diarrhoea. The skin turned pale and cold in spite of fever (39° C.). After 24 hours he had entirely recovered. At his next exposure 6 months later he reacted in exactly the same manner after 30 cc cow's milk. When he was 13 months old and had been admitted to the State Hospital in Oslo he was given milk progressively added to his food, to begin with by drops. Soon he tolerated fairly large doses. When at the age of $1\,^3/_4$ years the child was admitted to Crown Princess Lovisa Hospital

III: symptoms after hours

delayed allergic response

Cases Grouped According to Length of Latency Period	Symptomatology			
I VII &	v-d shock			
IX o	urticaria locally & erythema			
XI o	v-d urticaria »			
$XXI \ \Diamond$	urticaria »			
XXIII &	urticaria »			
XXII ?	v-d collapse			
XX 3 * - 1 1 2 2	edema of lips, stridor, asthma			
II XIV ♀ 10–15′	(v.) asthma			
X ♀ 15′	v-d shock edema of lips, cough, asthma			
XVII of 20'	shock urticaria-erythema (universally			
XIX ♀ 15–30′ 15′	v-d			
III VII 3 * - 1 1½-2	v-d shock urticaria (extensive)			
XXIII 9 1 2	v-d collapse			
I Q 2 2 2	v-d			
V \(\text{Q} 2 2	v-d collapse			
VI 3 2 2 2 2	v-d shock			
XIII & 2 2? 2	v.			
XXIV $\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	v-d shock (slightly shocked)			
II $\delta = 2\frac{1}{2} 2\frac{1}{2} 2\frac{1}{2}$	v. shock			
XV $3 \ 3-3\frac{1}{2}$	v. collapse			
XVI ♀ 3	v-d shock			
IV $3 * 4 < 4 2 2\frac{1}{2}$	v-d shock			
XII & 5 5—6	v-d fever & coughing			

in Stockholm cutaneous-intracutaneous tests disclosed specific hypersensitiveness to cow's milk only. The case was characterized as »obviously specific hypersensitiveness to cow's milk both in the digestive canal and in the skin».

report & catamnesis

Comments: At the ages of 2 and 8 months he was exposed for the first and second time to cow's milk, reacting after 5 and a little more than 5 (5—6) hours, respectively. At the age of 13 months he was progressively accustomed to milk but as late as 21 months the cutaneous sensitivity

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30	E		E	A			E	(A)	Str
19	E		E			_	-	-	Str
13 5	E		E		Ur		E	\mathbf{A}	v-d (eggs)
	E		E		1			-	
-	0	A			i	2 mo.	-	(A)	
_	2		?			_	-	_	Str
7-16	E	A	٠			† in asthma			
₹24	E			A	Rh	2	?	?	
93	E			\mathbf{A}		1 year	E	\mathbf{A}	\mathbf{Ur}
-	0			(A)			-	-	Ur
	0					-	-	passenge.	
1-4	\mathbf{E}			A		8 mo.			++ Str
-	0					-	-	dista	ste for eggs
_	0						-	recid	l. dyspepsia, till 7 yr
1	0		E			(1 weak)	E	-	
0	0		E		Ur			_	Str
2 - 3	0					until 13 mo.		-	
Accord 1	0					-	_	-	
America	0			A		?	-	-	
-	0							NAME OF TAXABLE PARTY.	
-	0		A	AA	Ur Rh			-	
$\frac{1}{2}$ -2	0						-	****	
0-5	0					?	7	?	7
	a fe	ew 1		1,	$1\frac{1}{2}$ —2 hrs	$\mathbf{E} = \mathbf{ecze}$ $\mathbf{A} = \mathbf{asth}$ $\mathbf{Ur} = \mathbf{urtic}$	ma		Str = strophulus Rh = rhinitis vaso- motorica

remained. After the end of the war the family returned to Norway. For this reason the later allergic history is not known.

Case XIII. CPLH 11/1946. Boy of 4 months without any allergic predisposition. When tasting cow's milk he reacted on every occasion with vomiting. When experimentally provoked at the hospital he was affected 2 hours later with violent fits of vomiting both after $^{1}/_{2}$ -milk and $^{1}/_{2}$ -citric-acid milk. Cutaneous test was considered superfluous.

Comments: From 5 to 13 months of age the infant kept reacting to cow's milk with vomiting, though gradually to a lesser degree. When 13—14 months old he had a transitory dry eczema on his cheeks which soon disappeared without any dietetic aid. Ever since he has tolerated cow's milk well.

CASE XIV. CPLH 137/1947. Girl, not quite 11 months old, with marked allergic heredity. The father and three other of his children have had asthma, as also the grandfather. While pregnant the mather had »eczema». She also suffers from hay fever. At the age of 5 months the child developed an eczema which became more and more even. sive. Eczematous elements grouped together here, there and every. where, first like »gneiss» round the scalp and in the face, then over the whole body. During the last month it became considerably worse and itched severely. No food consumed by either mother or child could be definitely suspected of aetiological significance. The child was now admitted because of her eczema and nutritive troubles. Stayed 72-On 3 occasions in the course of the autumn she had coughing attacks of an asthmatic type with stridulous and croaking respiration. Immediately after her first, tentatively given meal of gruel at the hospital she had an acute attack of asthma with cyanosis and pronounced dyspnoea, then vomited and collapsed, reacting badly, with a rapid though even pulse. Epicutaneous test negative, scratch test positive. Cow's milk, administered by drops, caused the eczema on one cheek to flare up for a day or so. Simultaneous antihistamine therapy proved an insufficient protection from attacks. At one time a dose of 50 cc 1/2-milk caused violent fits of vomiting and the eczema flared up everywhere, including the spot of the cutaneous milk test. Next time, the child vomited violently after 10 minutes, with an attack of asthma soon after. Only when administered orally was the antihistamine tolerance sufficiently increased. Finally, however, this therapy too was abandoned in favour of goat's milk, which was excellently sustained.

Comments: These attacks came on in less than a quarter of an hour beginning at the age of 11 months. This is the only case of ours where any antihistamine substance of a synthetic nature has been tried and abandoned in favour of goat's milk. The case is too recent to render a prognosis possible.

Case XV. Sachs' Children's Hospital (SCH) 193/1923. Male, breastfed infant admitted when $2^{1}/_{2}$ months old, as the mother contracted mastitis. Both mother and child stayed from 6/6 to 17/7. The mother's disease resulted in an abscess and the boy was given his first meal of cow's milk at 3 months of age (17/6). After 3 hours' latency he turned acutely pale and had violent vomiting attacks which gradually ebbed out into small fits of vomiting lasting for several hours. In the course

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of the afternoon his pallor increased. In the evening the pulse became bad. Next morning, immediately after the 7 o'clock meal, pulse, colour and general condition became affected. Stimulants had to be administered. The boy was given tea. During the forenoon he improved gradually. For the following 2 days he had fever (maximum 38.7° C. = 101.7° F.) and tonsillitis. By the third day he had recovered and was unaffected. With his second meal on 28/6 he was given an addition of 15 cc halfmilk and as before turned pale, vomiting after $3-3^{-1}/_2$ hours. He soon recovered, however. On the following day a hydrocele testis the size of a bean was discovered. During the period 4/7-11/7 desensitization with additions of small amounts of cow's milk was tried, rising from 1 gramme and 2-5 grammes to 10-30-75-75-150 grammes of 1/2-milk. When discharged the boy tolerated 170 cc 1/2-milk without any trouble. Neither on exposure nor during the treatment was any eruption noticed.

Comments: No hereditary predisposition. At 3 and 3 ½ months of age the boy had attacks. Latency 3 and 3 ½ hours, respectively. By means of small doses of cow's milk, progressively increased, he was brought in a week to tolerate milk without noticeable difficulty. After that he was not given milk until 8 months of age when he was easily weaned. Since then he has on no occasion displayed any allergic manifestations whatever. — A brother had mild asthma for a short time.

Case XVI. SCH 263/1923. Female infant was given mother's milk exclusively for 2 months with an addition of teaspoonfuls of caseinsodium during the third month because of a predisposition to loose stools. On account of the state of the mother's health weaning was then begun. At her first 1/9-milk meal the girl had only a few tenths of a cubic centimetre. None the less she reacted with violent fits of vomiting. On the other hand a mixture with cream was tolerated for several months. At the age of 7 months, 2 1/2-milk meals, 170 cc each, made her acutely sick after 3 hours with paleness, some cyanosis, violent vomiting, helonated eyes, but good pulse. After half an hour a large loose defaecation. Several hours later she was improving. Remained at the hospital 24/8-18/10. During one period, 15/9-22/9, she was given cow's milk in increasing doses, viz. 1-2-3-5-6-8-10 and $10 \text{ ce} \times 2$. Later, 20 ce × 2, 100 ce milk, 100-150-180 cc 1/2-milk. Well tolerated. The patient discharged on 200 mother's milk +1/2-milk $200 \times 2 + 200$ $^{1}/_{2}$ -milk-gruel \times 2, rusks, vegetables.

Comments: First attack at 2 1 /₂ months, second at 7 months of age. Then the latency was 3 hours. By careful administration she became accustomed to milk and soon sustained large doses without any trouble. In spite of massive allergic heredity the child has not since revealed the slightest reaction to milk nor any other allergic diseases.

CASE XVII. SCH 364/1923. Male infant, breast-fed until 6 1/2 months of age when he was given 200 grammes 1/2-milk as a first wearing meal but swallowed only 50 grammes. 20 minutes later the whole body assumed the colour of copper. The skin felt hot. The temperature was not taken. General condition unaffected. The next exposure took place 3 weeks later. 5 cc unboiled cow's milk was added to 100 cc mother's milk. Nothing happened until the next meal when the child refused to eat. When urged, he had 3 violent consecutive fits of vomiting. Colour and temperature of skin were normal. By cautiously adding fairly small quantities of cow's milk the dose was successfully increased from 1 to 50 drops without any reaction. After that 1 teaspoonful of milk was tolerated, but 2-2 1/2 teaspoonfuls provoked urticaria, pallor and vomit. ing. The child was now admitted to the hospital. A new attempt at desensitization therapy with gradual administration of cow's milk began. It was carried out with only a single interlude, viz. an urticarial attack provoked by a dose of 50 cc 1/2-milk.

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Comments: First attack when 6 $^{1}/_{2}$ months old. Latency 20 minutes. Later desensitized. In the course of the following years the boy tolerated milk excellently. During the first years he was fairly nervous and uneasy, rather disposed to cry. He reacted to eggs, berries and fruit with nettle rash. During later childhood free from eczema, asthma or other allergic manifestations.

CASE XVIII. SCH 245/1931. Girl, breast-fed. Admitted to the hospital when 6 months old together with her mother. Remained 2/2-15/10 1931. At the age of 4 months she had her first meal of cow's milk. After an hour or so she grew pale, had fits of vomiting. When 3 hours had elapsed, she became inert and somnolent, with a subnormal temperature of 36° C. and cold, livid hands and feet. At the following meal she vomited, then recovered. Temperature normal after less than 8 hours. On the following day cow's milk energetically refused. 10 days later (1/5) the patient reluctantly swallowed 5 cc 1/2-milk. The next meal of mother's milk provoked a violent fit of vomiting. General condition slightly affected. Skin normal. On 12/5, 2 teaspoonfuls of 1/2milk caused a violent vomiting fit after 2 hours' latency. On the fourth day of desensitization (11/5-24/5) after the administration of 50 cc cow's milk boiled for 10 minutes, another violent vomiting fit occurred. 21/5 general condition satisfactory; the patient able to consume 200 cc 1/2-milk without becoming sick. 12/6 condition unchanged.

Comments: First exposures when 4 and $4^{-1}/_{2}$ months old. Attacks after 1—3 and 2 hours' latency respectively. From the age of $1^{-1}/_{2}$ years the patient has been cared for by foster-mother. She has always tolerated milk, always been healthy and bright and eaten all kinds of food except eggs in any form, to which she has shown aversion.

CASE XIX. SCH 686/1946. Female infant admitted at appr. 8 months. Breast-fed, with a milk-free weaning meal daily. After the administration of cow's milk she always whimpered and in $^1/_4$ — $^1/_2$ hour vonited the whole meal. Her general condition was unaffected, however. From the time when she was 4 months old the mother had tried once a fortnight to administer cow's milk, but always with the same result. On the day of admission the girl was given 100 grammes milk with her evening meal and vomited all of it. Desensitization 23/7—27/7 without any trouble, apart from a fit of vomiting provoked after 50 grammes unboiled milk (26/7). Follow-up examination on 9/8 showed her to be completely rid of her trouble.

Comments: From 4—8 mos. the patient was tentatively given cow's milk once a fortnight but vomited each time after 15—30 minutes. »Desensitized» in a few days with a gradually increased amount of unboiled milk. Thereafter free from distress. During her second year neither eczema nor asthma.

CASE XX. The Samariten Hospital (SH) 846/1941. Boy 10 months old, the only child of healthy parents. For more than 7 months he was given mother's milk only. At the age of about 2 months an eczema developed localized to the body, extremities and cheeks. For this he was twice treated in the hospital when 3 and 4 months old. the age of 3 months, the somewhat scant supply of mother's milk was tentatively supplemented with cream and water. Almost instantly, after a couple of teaspoonfuls, his face became swollen, especially around the lips and eyes. He looked bad, sounded hoarse, breathed with difficulty, but recovered soon after being given a calcium tablet. About 4 months later a swelling was twice observed after mashed potatoes prepared with milk. When he was 8 months old, he was given ordinary infant's fare on doctor's orders. The first decilitre of milk provoked an attack similar to the first one. After an injection it passed off. The experiment was repeated with the same result. At the time of his admission his daily ration consisted of 4 meals of mother's milk with an addition of mashed potatoes and spinach, both prepared with mother's milk. His somatic and mental development corresponded to his age. The skin on the chin and lower part of the cheeks was dry and eczematoid, with slight changes around the eyebrows and on the extensor sides of right forearm and leg (between knee and ankle). On his first day in hospital he had an asthmatic attack without known cause and on the following day a severe attack of cyanosis. In both instances good results from adrenalin and stimulants. 2 days later an attack was provoked tentatively. A small quantity of cow's milk caused immediate vomiting and a minute or so later his respiration became stridulous. He was given still another teaspoonful of cow's milk per os. This he tried to get rid of by vomiting. After a quarter of an hour an attack of asthma set

in, culminating within an hour. Desensitization with a 10 per cont solution of cow's milk, boiled for 1 hour and administered by draps, was now tried. A week or so later the eczema on the cheeks was cured, It was treated only locally during the last few days (with tar). During the following month undiluted, long-boiled milk was continuously taken without any inconvenience until for a week the daily dose had been 50 cc (boiling time 2 hours). Then, unexpectedly, an extremely so gare attack of asthma, overcome only by injection of adrenalin +tonograph. occurred 1/2 hour after the porridge meal. All cow's milk was indue. diately withdrawn. When 10 days later an addition of 1 decilities of bouillon was tried, the infant quickly reacted with an asthmatic attack of the same severity. During the following week torantila treatment was started and continued from 2/2 to 21/2. A quarter of an hour offer the first injection universal urticaria broke out. On the following day only an edema on the dorsum of hands and feet remained. The eruption again manifested itself, totally disappearing on the second day. After this the child felt and fed better. The torantil was afterwards well tolerated and a new desensitization attempt was initiated on 18/2 with unboiled milk, dilution 1: 100. Blood eosinophilia, 7 per cent on admission, rose during the torantil therapy to 13 per cent, reaching a maximum of 16 per cent in the course of a subsequent desensitization trial with milk, then little by little falling (12-6-2 per cent). Within a month the dose was increased from 1 drop to 8 teaspoonfuls. Then the child again began to be troubled with asthmatic respiration and became subfebrile. Nevertheless the experiment was continued. The symptoms subsided, though periodically returning after intervals of 2 weeks. After 2 months the desensitization was discontinued on account of a catarrhal infection of the respiratory tract. It was resumed 4/5 to 28/5, when a new rhinopharyngitis set in. Vomiting and troublesome asthmatic fits accompanied this trial. According to a note in the record, on one occasion the eczema, though now cured, flared up 2 hours after administration of 16 drops of milk, the respiration simultaneously becoming asthmatic. At this point goat's milk was tried for a week but was not tolerated in the necessary quantities (100 cc). For this reason the child had to be sent home after almost 9 months' stay in the hospital to resume its milk-free diet. Lately this has brought about an improvement in the general condition and an increase in weight. Not until 2 months later was the child affected by asthmatic attacks. He died in the course of such an attack a short time after his discharge from the hospital.

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 $^{^{1}}$ Tonocard: *nicetamide* like circulation stimulant made by ${\it Astra},$ Sweden.

² Torantil (Bayer): desensitizing or anti-allergic substance from the mucous membrane of the small intestine.

Comments: The attacks, recurring at 3, 7, 8 and 10 months of age, appeared in immediate connection with exposure. Over a period of 9 months desensitization was attempted in every way, including medically, but without success. A fairly short time after his discharge the boy died in the course of a severe asthmatic attack. No information is available as to whether or not this was provoked by milk. On one occasion beef tea had the same allergenic effect as cow's milk. This experience corresponds to Schlossman's experiment with bovine serum.

CASE XXI. SH 902/1941. This case concerns a girl a little more than 6 months old admitted because of eczema. The mother also had severe eczema as a child. This, however, is the only known allergic manifestation in the family. For a few months back the girl has had a milk-free weaning meal, otherwise being fed from the breast only. Lately she has developed a dry eczema on the arms and in the face. During the past few days the eczema has become weeping and in connection with this aggravation it has also extended over the body, the skin of which at the time of admission is dry and reddish. In the capillitium and on the cheek the eczema was covered with fat dried crusts. The rough skin of arms and legs showed some marks after scratching. Local tar treatment achieved some improvement after a couple of weeks and complete cure a little more than a month later. A fortnight after her admission additions of cow's milk were tried. From the first urticaria appeared on neck and breast after such a meal. With an increased addition a transitory inclination to vomiting occurred, but on no occasion was there diarrhoea, shock or asthma. The case appeared to be one of purely cutaneous hypersensitiveness. Since her discharge the girl has been healthy. The eczema has altogether vanished, nor have any other allergic diseases appeared since.

Comments: At 7 months of age cow's milk per os provoked an immediate attack of urticaria. Simultaneously with weaning the eczema grew temporarily worse, then disappeared. No asthma or urticaria has developed in childhood. The child has tolerated milk without any general or cutaneous reactions ever since. She has, however, always had an aversion to milk and also to eggs.

Case XXII. SH 58/1946. Female infant, 6 months old. On 2 of 4 occasions when exposed to mixtures of cow's milk she vomited and collapsed. First it was thought that »something had stuck in her throat». However, the district doctor, who was summoned on the next occasion, remitted the girl to the hospital, diagnosing her distress as idiosyncrasy to cow's milk. While at the hospital she was repeatedly fed with milk. On the first occasion she was slightly affected and turned exceedingly pale but later she failed to react.

Comments: Data regarding latency vague but the reaction evidently appeared rather quickly, within a maximum of a few minutes. Since her discharge she has had no attacks of the idiosyncrasy. Only on some isolated occasions has the respiration had an asthmatic character (in connection with colds?). Fruit, especially strawberries, provokes skin eruptions.

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CASE XXIII. SH 735/1946. Boy of 6 months. He had no allergie predisposition. However, in connection with a cold 3 weeks before his admission he developed asthmatic troubles which recurred on the day before his admission when he had a fresh cold. During the preceding weeks he had diarrhoea, which was treated with tea starvation and bil. berry soup. When admitted he had an asthmatic attack. This abated in a few minutes, however, after administration of adrenalin. He is said to have been unable earlier to tolerate cow's milk, but additions of unboiled or boiled milk in gradually increased doses have not produced any gastro-intestinal or general reactions. Nor have the asthmatic troubles recurred. On the other hand, he disclosed an obvious cutaneous hypersensitiveness. Whenever in the course of feeding the skin happened to come into contact with unboiled cow's milk a strongly reddish area. the size of the palm of a child's hand, at once appeared extending from the left corner of the mouth down the neck and fading little by little during the following hour.

Comments: At the hospital the boy reacted to cow's milk merely with erythema. During the following two months or so at home he vomited every time he drank cow's milk. After that time this symptom ceased, as did the contact erythema also. For still another 6 months his respiration became somewhat asthmatic when he was affected by a cold though decreasingly so until finally this trouble completely disappeared. The history of the case leaves the impression that no direct connection existed between the asthmatic troubles and the exposure to milk.

Case XXIV. Female infant, first child of healthy parents of nonallergic families. When she was 3 $^1/_2$ months old she had been exposed to cow's milk only twice. On the second occasion the dose was limited to $^1/_2$ teaspoonful. Both times vomiting and diarrhoea occurred after 2 $^1/_2$ hours. The child was pale and did not fall asleep as usual after the meal. Experimentally a drop of milk boiled for 20 minutes, was administered. After 2 $^1/_2$ hours the child had a fit of vomiting and felt sick. The skin felt hot. By means of small, slowly increased doses of milk diluted 1: 10 tolerance to large doses was gradually achieved.

Comments: On 3 occasions before reaching the age of 4 months the girl reacted with violent fits of vomiting, diarrhea and slight shock, each time after a free interval of $2^{1}/_{2}$ hours. Milk was administered by drops

in gradually increased doses and the idiosyncrasy was overcome. Other allergic manifestations have not occurred. There were no hereditary allergic affections.

Discussion

If one considers these 23 disease histories in detail there is one feature that is striking. The shock or its equivalent always develops rather acutely, but only in about half of the cases in close conjunction with exposure to the allergen. By »close conjunction» we mean within the first 20 minutes, as a rule not more than 5 minutes after exposure. In rather more than 50 % of the cases there is an appreciably longer symptom-free interval during which the infant shows at the most some small discomfort. This latency time is most often 2 or 3 hours, but in exceptional instances it may be 4—5, possibly 6 hours (SHICK and PESHKIN give even up to 24 hours).

In individual cases the period of latency need not be the same from one attack to another. In some 1/5 of our infants the period varied on different occasions, e. g., 2 or 4 hours according to circumstances (No. IV) or with a tendency to longer free intervals with increasing age (No. VII and XX). Nevertheless in 3/4 of the cases one could reckon on finding the same period of latency in a new attack as in the one or more preceding — even when several months had elapsed since the last reaction against cow's milk. Thus if in January an infant had violent vomiting 3 hours after drinking 1 decilitre of *\(^1/2\)-milk*, then in March or April when it was next exposed to the allergen in one formula or another it would again vomit after a 3 hour delay. This, of course, provided the idiosyncrasy had not disappeared in the meantime, either spontaneously or as a result of treatment.

The clinical course of the attack is sufficient to determine the diagnosis in many cases, but as a rule it is desirable to verify the diagnosis by as complete tests as possible. The doctor must be on guard, however, against the subsidiary effects of these tests, which may occasionally involve actual danger to the patient. The violent reactions of patient No. VII both to attempts at exposure and to intracutaneous tests may serve as an illustration of this point: all such tests involve a certain element of risk for the patient concerned and this applies equally to infants.

It is perhaps in this connection that Prausnitz-Küstner's reaction has its greatest merit. By transferring the patient's serum to another person who is not allergic, the risk to the tient is removed; one so to speak transplants the possibility of shock to a quarter where it cannot make itself felt. Moreover, it is unquestionably the most reliable and specific test we possess. It fails only when the antibody does not circulate in the plasma but occurs only in the tissues and is incorporated in them. In such an event it is replaced by the test worked out by URBARH at the suggestion of KÖNIGSTEIN, in which tissue fluid for interdermal injection is produced through the formation of swelling The principle is otherwise identical in these 2 procedures. As regards technique, see URBACH and GOTTLIEB. Another respect in which this reaction differs from that of Pransnitz-Küstner is that reddening and the infiltrate come out not in the course of the first 2 hours or so but only after 12-18 hours. maximum 24 hours, as in the Mantoux test. The histology of the tissue reaction also corresponds to that of Mantoux: an inflammatory process in which the cellular infiltrate dominates in the picture and the extravasate is less pronounced. URBACH refers to it as »the delayed-inflammatory reaction».

Recently LINDEBERG-LINDVET has advocated a more extensive use of the leucopenic index in the diagnosis of foodstuff allergies. He imposes quite severe demands with regard to the execution of the test, however, — so severe that it is hardly possible to fulfil them, since among other things it is not possible to keep an infant quiet before and during the test. And with these infants I do not believe it is absolutely necessary to take blood samples for leucocyte count in the morning only, as their mealtimes are fairly evenly distributed over the 24 hours. Our tests at Norrtull were made at the second meal of the day and it was our impression that the fall in the number of leucocytes could in any case be sufficiently large to be distinctly interpreted (Nos. VII and IX). In case VII the difference between the results before and after the desensitization trial was striking.

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EXPOSURE TRIAL WITH DETERMINATION OF LEUCOPENIC INDEX.

Pat. VII:

- 21/3 11.30 a. m.: 9 200 leucocytes/mm³. Following that 5 g and 10 min. later a further 50 g uncooked cow's milk.
 - 11.50 a.m.: 9 200 poly 5 000+mono 4 200.
 - 12.30 p. m.: 7 750: 3 300+ 4 450. At this time a large splotchy erythema appeared on body, face and scalp. The infant suffered slightly from shock.
- 23/3 Intra-cutaneous test made with milk. After barely 2 hours the local and universal reaction: a large spotted eruption similar to that 2 days before and incipient shock which was checked by adrenalin and *nicetamide*.
- 25/3 Desensitization trial begun according to plan (see table 2). This took 2 weeks and the only subsidiary effect of this administration of milk may possibly have been more frequent motions on the eighth day of treatment.
- 11/4 The test of 21/3, with determination of the leucopenic count, was repeated: double determinations, double counts were made both just before and 20 and 60 minutes after giving 60 cc cow's milk per os. No definite fall in the number of leucocytes was found and no general reaction was provoked.

Prausnitz-Küstner test was made twice: first on 1/4 (= eighth day of treatment) and again on 11/4. The tests were made according to the description by von Sydow. The allergen, 1 cc milk, was injected intramuscularly after 24 hours. After 30 minutes an intense local itching arose in the skin followed by a papule 30×40 with redness 50×70 mm. In addition, headache lasting several hours. When the test was repeated 11/4 on two persons, there was no reaction (4 hr. observation).

Pat. IX:

- 8/5 46: Leucocytes 16 000, poly 3 900+mono 12 100 before giving 20 g milk.
 - » 10 900, poly 3 100+mono 7 800, 20 min. after exp.
 - 12 150, poly 2 750 + mono 9 400, 40 min. after exp.
 - 12 700, poly 3 800 + mono 8 900, 60 min. after exp.
- 9/5—19/5 desensitized again. The skin allergy to milk was then (and as long as we could follow up the case) gone. Unfortunately we had no later occasion to make fresh determination of the leucopenic index. Prausnitz-Küstner was negative even before desensitization.

In conjunction with the Prausnitz-Küstner test - or, as it is also called in Urbach, "the passive transfer test" - on patient No. VIII, a condition arose which may occasionally constitute a considerable disadvantage in this form of testing and which in this case was due to the fact that the infant had severe eczema and consequently, as is usual with eczema children. was also allergic to eggs (Gezelius 1938). When the person to whom the passive transfer had been made ate egg a week after the test, there was again local reaction and this time far stronger than on exposure to milk. In addition to the local reaction there was a large edema in the arm and local pain lasting a day, together with headache. It is probable that similar reactions may occur after appreciably longer periods - I have found no exact indications as to how long. The reaction arose despite the fact that both the original test and the accessory reaction were performed with the Walzer modification of the Prausnitz-Küstner test.

The arbitrarily selected desensitization programme (table 2) was found in 3 cases to function with the utmost satisfaction: in 12-14 days a change from definite positive allergic test to negative reaction was evident, clinically the allergy had disappeared and the mother could continue to give the infant milk at home without any obvious risk of relapse. The change seemed to set in somewhere in the middle of the second week of the »desensitization», but the exact point of time we have not yet been able to determine in a satisfactory manner. One is not warranted in drawing conclusions merely, from the 3 isolated cases treated. It is conceivable that this programme applied to larger material will furnish similarly satisfactory results. Moreover, it may well be supposed that by giving the desensitization doses of allergen at much shorter intervals (10-20 small doses/day) one may attain the same tolerance in a few days, where it took us 2 weeks. For us it was an advantage to have a little longer time to enable us to follow the course more accurately.

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Table 2.

Dose

lst	day:	milk/water	10	%, boiled	60':	5 +	10+	- 20	ee	=	1-	1 -1	- 2	g	milk	
2nd	9	19	10	%, boiled	40':	5+	10+	- 20	cc	==	1 1	-1-	- 2	g	milk	
3rd	20	19	20	%, boiled	30':	5 +	10 +	- 20	ee		1 4	- 2 -	4	g	milk	
4th	9	39		boiled	20':	10-	-20+	40	ce		2 -	-4-	-8	g	milk	
5th	p				15':	10 +	-20+	-40	ee	===	2 -	4 -	-8	g	milk	
6th				1.00	10':										-	
7th		3		-	8':							_		-	-	
8th	à	19			5':									-	-	
9th	10	10			$3\frac{1}{2}'$:											
10th	10	19			2':											
11th	ō.				1':											
12th	9				12:										-	
13th	15				(+)		-				****		-			
14th	16	19		unboiled	0'						2 -	- 4 -	8	g	milk	

Programme for desensitization by mouth.

After 14 days rapidly increasing doses (50—100—150 gm/day) are given of the formula the infant is to continue to have. The mother is instructed not to neglect giving the infant milk on any day in the next six months.

Prognosis

The particulars of allergic manifestations in the later lives of the patients, which were obtained by questioning the parents, are given as a commentary after each journal report, together with some main features of the earlier course of the disease. They are partially presented against the most typical conditions in the actual course of the disease in a summary survey (table 1).

The cases here have been grouped according to length of latency time for attacks. They fall naturally into 3 groups which also display other noteworthy differences in relation to other factors of the disease.

The first group comprises all cases in which exposure to cow's milk causes immediate allergic reaction, no matter what the nature of the shock tissue. One might also include patient VII in this group, since he, at least in his first attack, reacted

^{3 48547} Stephan Vendel

immediately. The gastro-intestinal reaction was in only 4 of these 8 cases predominant in the attack, and in 4 out of 8 contact between the intact skin and the cow's milk allergen caused an urticarial outbreak; it might be called a contact erythema or a contact urticaria. It is characteristic for this group that all except a single one had typical infantile eczema (as a rule with pronounced eosinophilia). 2, moreover, had asthma, which in one case was independent of the milk allergen, but in the other case could be brought out by cow's milk and in fact had a fatal course after a few months. The eczema heredity (and other allergic heredity) was much stronger in this group than in group III. As regards the later course, these children, like all other eczema children, usually retained their eczema for one or more years, though as a rule the cow's milk idiosyncrasy had already passed, at the time of discharge or a month or 2 after. Where cow's milk provoked asthma, the allergy seemed to disappear later than in the other cases. The majority of children in this group later developed hypersensitivity to the most varied kinds of fruits, berries, fish and so on — usually evidencing itself as a strophulus.

As may be seen from the last group, group III, it is striking that the individual infants maintained their individual latency time from attack to attack; but despite several hours latency the attack occurred with the same violence and suddenness, when eventually it arrived, as in the case of the children in group I. The symptoms were linked with the digestive tract and the circulation. Asthma did not occur in this group. When an attack took place the skin was, so to speak, "dumb". This is in agreement with the observation reported by Schick and Peshkin that cutaneous tests are negative in patients in whom the allergic reaction presents itself a long time after exposure.

Moreover, these infants had no eczema at the same time or later in childhood (No. VII again the exception, as also No. V), and follow-up study indicated that only quite exceptionally did they acquire other allergic manifestations in the course of childhood (strophulus in one patient — and that merely episodic). Where a differential count was made, no eosinophilia was found worth mentioning.

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Group II constitutes a transition between the 2 other groups: the 2 infants with shortest period of latency (less than 20 minutes) both reacted by asthma attacks and vomiting, and had eezema, definite eosinophilia, and an allergic heredity of asthma. In the 2 others of the group the bronchi were not among the shock organs and neither had eczema. Thus they were more nearly allied to group III.

If on the basis of the above one is to make a prognosis in a case of cow's milk idiosyncrasy, one is of course aware that it is as a rule of but few months' duration. Nevertheless, by means of the desensitization process one may actively contribute to shortening this course to a couple of weeks or less. A lethal course is quite unusual (see, however, No. XX and also cases published by Anna Helmer). What is first of all required to assess the prognosis is the whole development of the infant during child-hood; but where there appear at the same time other expressions of allergic constitution — chiefly eezema and asthma — in an infant and where possibly there also exists a massive allergic heredity, it will be these circumstances, independent of a cow's milk idiosyncrasy occurring at the same time, that will be decisive in judging the general allergy prognosis for the later childhood of the infant.

Nevertheless it seems possible to draw certain prognostic conclusions from the symptomatology and course of even a single case of cow's milk idiosycrasy. The mere occurrence of cow's milk allergy in a child in itself means nothing, however, concerning the probable likelihood or unlikelihood of other allergic manifestations.

Conclusion

Cow's milk idiosyncrasy seems to appear in 2 basic clinical types, the most striking difference between them being the period of latency of the allergic reaction. — In one case the attack comes (several) hours after exposure to the allergen and the shock reaction is associated with the intestines and circulation organs, leaving the skin and respiratory tract intact. This group of infants is otherwise but little allergic on the whole.

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As may be seen from the last group, group III, it is striking that the individual infants maintained their individual latency time from attack to attack; but despite several hours latency the attack occurred with the same violence and suddenness, when eventually it arrived, as in the case of the children in group I. The symptoms were linked with the digestive tract and the circulation. Asthma did not occur in this group. When an attack took place the skin was, so to speak, "dumb". This is in agreement with the observation reported by Schick and Peshkin that cutaneous tests are negative in patients in whom the allergic reaction presents itself a long time after exposure.

Moreover, these infants had no eczema at the same time or later in childhood (No. VII again the exception, as also No. V), and follow-up study indicated that only quite exceptionally did they acquire other allergic manifestations in the course of childhood (strophulus in one patient — and that merely episodic). Where a differential count was made, no eosinophilia was found worth mentioning.

Group II constitutes a transition between the 2 other groups: the 2 infants with shortest period of latency (less than 20 minutes) both reacted by asthma attacks and vomiting, and had eczema, definite eosinophilia, and an allergic heredity of asthma. In the 2 others of the group the bronchi were not among the shock organs and neither had eczema. Thus they were more nearly allied to group III.

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If on the basis of the above one is to make a prognosis in a case of cow's milk idiosyncrasy, one is of course aware that it is as a rule of but few months' duration. Nevertheless, by means of the desensitization process one may actively contribute to shortening this course to a couple of weeks or less. A lethal course is quite unusual (see, however, No. XX and also cases published by ANNA HELMER). What is first of all required to assess the prognosis is the whole development of the infant during childhood; but where there appear at the same time other expressions of allergic constitution — chiefly eczema and asthma — in an infant and where possibly there also exists a massive allergic heredity, it will be these circumstances, independent of a cow's milk idiosyncrasy occurring at the same time, that will be decisive in judging the general allergy prognosis for the later childhood of the infant.

Nevertheless it seems possible to draw certain prognostic conclusions from the symptomatology and course of even a single case of cow's milk idiosycrasy. The mere occurrence of cow's milk allergy in a child in itself means nothing, however, concerning the probable likelihood or unlikelihood of other allergic manifestations.

Conclusion

Cow's milk idiosyncrasy seems to appear in 2 basic clinical types, the most striking difference between them being the period of latency of the allergic reaction. — In one case the attack comes (several) hours after exposure to the allergen and the shock reaction is associated with the intestines and circulation organs, leaving the skin and respiratory tract intact. This group of infants is otherwise but little allergic on the whole.

In contrast to this *pure* form is the other type, where the acute cow's milk allergy's classic syndrome is mixed with or partially replaced by urticaria and asthma; and where all reactions blaze up with a latency period of a few minutes or seconds. In this instance one may assume that the patient is an all-round developed allergical subject, in whom the cow's milk idiosyncrasy is merely one detail in the mosaic, even though it constitutes a significant feature.

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Summary

In the period 1919—1947 a total of 23 clinically definite cases of cow's milk idiosyncrasy were treated at the 4 children's hospitals of Stockholm. This series of cases, supplemented by one case from private practice in Stockholm, is surveyed and attention is directed to an unusual symptom to which earlier authors have not attached any great significance, namely the very varying interval of time between exposure and allergic reaction. It is found that this allergic period of latency is as a rule individually constant and that therefore with this basis of classification it is possible to present the 24 cases so that their other clinical symptoms fall naturally into two distinct clinical types. These two types agree with the classification of cow's milk idiosyncrasy which von Sydow, on other grounds, has proposed.

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¹ Winge Flensborg, in oct. '48, has informed me about the concept of Schloss, who (in 1920: Am. J. Dis. Child) distinguished 2 types of cow's milk allergy stressing the difference in time between exposure and reaction of the two groups.

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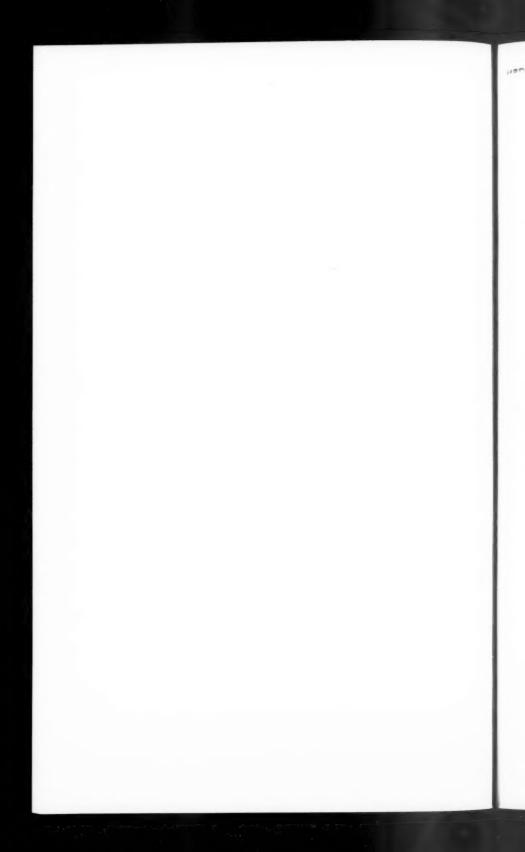
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ACTA PÆDIATRICA

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KRONPRINSESSAN LOVISAS BARNSJUKHUS,
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FROM THE SACHS' HOSPITAL FOR CHILDREN (HEAD: DOCENT J. HENNING MAGNUSSON M. D.) AND THE CHEMISTRY DEPARTMENT II (HEAD: PROFESSOR J. ERIK JORPES M. D.) OF THE CAROLINE INSTITUTE, STOCKHOLM, SWEDEN.

PEPTIC AND TRYPTIC CAPACITY OF THE DIGESTIVE GLANDS IN NEWBORNS

A COMPARISON BETWEEN PREMATURE
AND FULL-TERM INFANTS

BY

BIRGITTA WERNER

ACTA PÆDIATRICA, VOL. XXXV, SUPPLEMENTUM VI

Stockholm 1948

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Translated by ERICA ODELBERG

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Introduction.

The favourable results obtained in recent years by supplementing the food of premature infants with protein hydrolysates instead of whole protein (Magnusson 1944) call for a closer study of the proteolytic enzyme system in the digestive tract of these infants. Investigations carried out recently at the Sachs' Hospital for Children (Jorpes, Magnusson and Wretlind 1946) have shown that while the full-term infant to a considerable extent utilizes a supplement of casein to its ordinary food of breast milk, the premature infant is severely handicapped in this respect. Casein hydrolysates, on the other hand, are utilized equally well by both classes of infants. As in these investigations the supplement administered varied only as to whether the protein was split or not it appeared most likely to attribute this insufficiency of the premature infant to a developmental deficiency of its proteolytic enzyme system. The question then arose as to whether it was possible to demonstrate a morphological basis for this deficiency.

The literature shows that while the secretion of hydrochloric acid in newborn premature and full-term infants is fairly well investigated, our knowledge of the proteolytic enzyme system of these infants is very incomplete. Thus SMITH, for instance, as late as 1946, after discussing the secretion of hydrochloric acid in the stomach of full-term infants, wrote: "So much less attention has been devoted to the other digestive substances in the newborn stomach that only a brief statement can be made concerning pepsin and rennin. The glands secreting them are present at birth and well before, and the substances are measurable neonatally, though in perhaps lower concentrations than in later infancy."

In this treatise the writer has tried, by analyzing a fairly large number of cases with histological and chemical methods, to elucidate the developmental stage of the pepsin and trypsin-producing cells in newborn premature and full-term infants.

PART I.

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PEPSIN.

Review of the Literature.

Pepsin in Relation to the Chief Cells and their Granules.

In 1834, both Beaumont and Eberle showed that the gastrie juice has protein-splitting properties. Two years later, Schwaxx named the active principle pepsin. It has long been known that pepsin is produced by the chief cells of the main gastric glands. glandulae gastricae propriae. As is well known, three types of gastric glands are distinguished: the cardiac, surrounding the cardia; the pyloric, in the pyloric region; and the main gastrie glands in the body of the stomach. Starting from their openings in the bottom of the gastric pits, the densely arranged main gastric glands can be divided into the isthmus, the neck and the body. The layer of mucous cells covering the inner surface of the stomach and the walls of the gastric pits continues unbroken through the isthmus into the neck, to be intermingled there with mucous cells of a special nature and solitary chief cells (Hauptzellen — Heidenhain, Adelomorphe Zellen — Rollett). As the neck merges into the body, the chief cells rapidly grow more numerous, to become dominant around the lumen of the lower two-thirds of the gland. Behind the layer of chief cells lie the parietal cells with their intracellular canaliculi opening into the lumen of the gland.

These two types of cells in the main gastric glands were first described by Kölliker (1854). Twenty years later Heidenham and Rollett—independently of each other—subjected them to a closer study. Heidenham came to the conclusion that pepsin was produced in the chief cells, now called zymogen or peptic cells. The amount of corroborative evidence accumulated in the litera-

ture since then seems to furnish sufficient proof for the accuracy of this assumption. Heidenhain himself observed that unmistakable changes took place in the chief cells during different stages of digestion and with varying pepsin content of the gastric mucosa. As no such changes could be seen in the parietal cells - an observation confirmed by GRÜTZNER (1875) - he concluded that pepsin was formed in the chief and not in the parietal cells. This was in disagreement with several other workers, who had - on less convincing grounds - held the opposite view (HERREN-DÖRFFER 1875, WOLFFHÜGEL 1876 and NUSSBAUM 1877). SWIECICKI (1876) threw more light on the subject by his investigations on frogs, in which glandular cells resembling chief cells are present in the oesophagus. He demonstrated that if the lower part of the oesophagus was ligated, pepsin could be obtained from the oesophagus, but hydrochloric acid from the stomach only. Lim (1922) confirmed the presence of pepsin-producing cells in the oesophagus of the frog. Bowie later stained these cells by his special method (p. 25) and found granules of the same type as in the chief cells of mammals (FRIEDMAN 1937). In 1878, SEWALL showed that no pepsin could be demonstrated in the sheep prior to the development of the chief cells. In 1934. LINDERSTRØM-LANG and collaborators estimated the pepsin content of the gastric mucosa in microtome sections laid parallel to the surface of the mucosa. They were able to demonstrate convincingly the close relationship between the chief cells and the production of pepsin. These determinations were carried out in such a way that the peptic activity in one section was determined chemically and compared with the number of chief cells present in the next lower section. It was found that the pepsin content was highest in the body of the stomach and there in the basal part of the mucosa, where the greatest number of peptic cells are to be found, and diminished towards the neck of the gland. with the decrease in number of the chief cells.

The characteristic granules of the chief cells were first described by Langley & Sewall (1879), who investigated them in a number of animals. In the rabbit a comparison of the gastric mucosa of starving and digesting animals disclosed a relation between pepsin and granules. The mucosa of the starving animal was rich in granules, and showed a high peptic activity, while a sparsity of granules and a lower pepsin content were characteristic of the digesting animal. Moreover, in the same animal the denseness of the granules was not uniform throughout the mucosa, and an area rich in granules invariably exhibited a high peptic activity, while scanty granules always coincided with a low peptic activity. These results were confirmed by others (Green wood 1822, Noll & Sokoloff 1905 and DI Christina 1908).

The study of the granules in the chief cells was, however, greatly impeded until Bowie found a reliable method for fixing and staining them. Using this method Bowie & Visiberral (1935) convincingly demonstrated the close relationship between granules and pepsin, and the term pepsinogen granules—now in general use—should therefore be correct. Since the present writer using Bowie's staining method has taken the granules of the chief cells as a criterion of their degree of maturity, it should be of interest to describe briefly the experiments of the aforementioned writers.

Their experiments were carried out on well-nourished dogs in three ways. The animals were anaesthetized throughout the experiment. In each case a metal cannula was inserted through an incision in the stomach wall and a piece of the gastric mucosa excised from the body of the stomach for histological examination as to the initial picture. With Bowie's staining technique it showed abundant pepsinogen granules.

In the first experiment secretion was induced by hourly injections of histamine, and the secreted juice collected. After eight hours another piece of mucosa was excised for histological examination. No change in the amount of granules as compared with the initial picture could be observed. The mucosa was still rich in pepsinogen granules. The highly acid juice secreted during this eight-hour period was poor in pepsin. This experiment was repeated seven times.

In the second variation secretion was induced by rhythmic electrical stimulation of the vagus nerve for a period of several hours. A control piece of mucosa excised after this time showed

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a marked decrease in the number of granules, as compared with the initial sample. After eight hours' stimulation the granules were found to have disappeared completely. The total amount of pepsin in the juice obtained in this experiment was far higher than in the histamine experiment. This experiment was repeated in eight animals.

Finally, in the third experiment (in three animals) secretion was induced by repeated injections of histamine for several hours, followed by prolonged faradic stimulation of the vagus nerve. After the histamine injections the mucosa exhibited abundant granules, as in the previous histamine experiment, while vagal stimulation was even here found to empty the mucosa of granules. The juice was poor in pepsin after histamine and rich after faradic stimulation.

From this review of the literature it is evident not only that the site of the formation of pepsin is the chief cells—a fact now generally accepted—but also that there is a very close relation between the granules in the chief cells and pepsin. For this reason it appears justifiable to consider the presence of granules stainable according to Bowie as a sign that the chief cells in question are capable of producing pepsin.

The Foetal Development of the Peptic System.

Investigations on man.

Elsässer (1846) showed that the gastric mucosa of stillborn infants could digest protein. Since then the development of the pepsin-producing apparatus has been the subject of numerous investigations both in man and in animals. Notwithstanding the valuable work done on this problem, it cannot be said that we have today a clear picture of the developmental stage of the pepsin-producing system in newborn infants.

Our lack of knowledge on this subject may be attributed to a variety of factors. The material of earlier investigators was usually obtained at the ordinary post-mortem several hours after death. The consequence of this is well illustrated by a quotation from Baginsky (1882): "Die Untersuchung des Magens bietet beim Kinde deshalb besondere Schwierigkeit, weil es fast nie glückt, die ganze Schleimhaut wohlerhalten zu finden. In der Regel sind Cardia und Fundus zum Theil des Epithels beraubt, stückweise die Schleimhaut fast verloren gegangen oder maceriert." The interval elapsing between death and the preparation of the specimen was considerable even in investigations made as late as in the present century. In Schmidt's material (1914) it was 14—40 hours and in Keene & Hewer's (1929) 12 hours. Bloch (1903), it is true, fixed the preparation immediately after the infant's death (p. 13) but his method was not well suited for preserving the granules of the chief cells. Miller (1941) commenced fixation half an hour post mortem, but did not study in detail the peptic cells, which are of interest in the present investigation.

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The zymogen granules, so characteristic of the functioning chief cell, are difficult to preserve and stain. Consequently, many earlier investigations suffer from an imperfect histological technique. It was not until Bowie elaborated his method that this difficulty was overcome. Finally, it will be evident from the writer's summary of the literature that the number of cases examined has usually been small—in fact, conclusions have often been drawn from the analysis of a single case (Table 1).

Table I. Number of Cases in Earlier Investigations Pertaining to this Work.

	Prema	ature		
	late	early	Full-term	Total
	foetal 1	nonths		
Elsässer1846	?		?	?
HAMMARSTEN 1874	1	*****	9	10
ZWEIFEL	1	1	6	8
LANGENDORFF1879		6		6
FOLDT1880		2	-	7
BAGINSKY1882	1	_	1	*)
JAKUBOWITCH1898	?	7	2	?
Вьосн1903	*****	-	3	3
SCHMIDT	1	- Marine	3	4
Scотт1925	9	?	2	?
KEENE & HEWER 1929	From the 46	th foetal mo	onth to term.	13
MILLER1941	6	-	4	10

The investigations referred to in Table I, which comprise the most important works on the development of the pepsin-producing apparatus in man, require more detailed consideration.

Hammarsten, Zweifel, Langendorff, Jakubowitch and Keene & Hewer all investigated the peptic capacity by chemical methods. Hammarsten found that the gastric mucosa of full-term infants was richer in pepsin than that of any newborn animal (dog, cat, rabbit) examined by him. He could find no pepsin in a human foctus of seven months.

ZWEIFEL found pepsin in all his full-term cases and also in an infant "etwas zu früh geboren," but none in an embryo of four months.

Langendorff's material consists exclusively of early embryonic cases and is therefore of little interest for this work, which aims at a comparison between the proteolytic enzyme system of full-term and viable premature cases. He found peptic activity as early as in the fourth embryonic month.

JAKUBOWITCH mainly investigated somewhat older age groups (5 days to 12 years) with the intention of ascertaining how the enzymatic activity was influenced by various diseases. Premature cases were presumably included in his material, since he states that pepsin can be found in full-term as well as in premature infants. Unfortunately, he does not state the number and condition of the cases on which he bases this conclusion.

KEENE & HEWER made a qualitative investigation of how early in foetal life the various digestive enzymes could be demonstrated. Taken as a whole, their material was fairly large (37 cases) but peptic activity was investigated in 13 cases only. These cases, all of which showed pepsin, varied in age from the fourth foetal month to full-term. These authors supplemented their investigation with a histological examination of the gastric mucosa. They found that three types of cells could be differentiated in the main gastric glands in the fourth foetal month: mucinogenic, parietal and peptic cells.

Schmidt examined the pepsin content of the stomachs of four newborn infants who had died before or shortly after birth. Of these, three were full-term infants and one a premature weighing 2 200 g. He used a quantitative method (Fuld's turbidity method). Since, however, only one of his cases was premature, and in addition the material was examined a considerable time after death, his results cannot be of great value. He found high pepsin values in two of the full-term cases, corresponding according to his calculations to 20 per cent of the values in an adult. The premature infant had a pepsin content corresponding to 50 per cent of that of the full-term cases. The third full-term infant, however, showed considerably lower values than the premature infant.

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Instead of post-mortem examination of the gastric mucosa. MEYER (1902), REEVE-RAMSEY (1908), Andersen (1935) and others examined the gastric juice in newborn but only full-term infants, and found pepsin in all cases.

All the investigations discussed in the foregoing (with the exception of those of SCHMIDT) are of a qualitative rather than a quantitative nature.

Histological methods were applied to the study of the development of the gastric mucosa in man by Toldy, Baginsky, Bloch, Scott and Miller.

All these workers were, for one reason or another, interested in the differentiation of the cells in the main gastric glands, but none of them paid special attention to the granules of the chief cells, a structure of prime importance for conclusions concerning the state of maturity of these cells.

TOLDT, who was mainly interested in the semi-macroscopic structure of the glands, stated that the chief cells can be found as early as in the fifth or sixth foetal month; he did not mention how many cases were included in his material, nor any details of the cells studied.

BAGINSKY examined two cases only, one full-term and one premature, born in the seventh foetal month. He could see no differentiation of the cells in the main gastric glands of the premature case but found well developed types of cells in the full-term one.

BLOCH examined three full-term infants, two stillborn and one who died four days after birth. He found the chief as well

as the parietal cells "vollständig entwickelt." He fixed his material in situ by injecting formalin into the abdominal cavity immediately after death, thus avoiding difficulties due to autolytic processes in the mucosa. He mentions the granules in the chief cells but complains of their being unsatisfactorily stained—a finding well in accordance with that of other workers who have used formalin as a fixative for zymogen granules. For this reason no special interest is focused on the granules in his final discussion. He mentions that granules are sometimes present and sometimes lacking.

Scott's work has no direct relation to the problem discussed in this treatise, but is nevertheless of indirect interest since he followed the development of the gastric mucosa by calculating the number of crypts and glands per unit surface area in various age groups. He found a considerably more rapid increase in the number of glands during the first third of the last foetal month than in any other period.

MILLER studied the secretion of hydrochloric acid in various age groups, and in this connexion examined histologically the development of the gastric mucosa in ten cases — six premature and four full-term ones. He did not directly mention the chief cells but found the general picture of the gastric mucosa of cases weighing less than 1 800 g at birth to be of a very primitive type as compared with that of full-term infants.

Investigations on animals.

In contrast to man, animals have been examined in detail and on fresh material. Thus examination of large series of dogs has shown that the canine gastric mucosa contains no pepsin until two weeks after birth (Hammarsten 1874, Wolffhügel 1876, Langendorff 1879, Gmelin 1904). Gmelin supplemented his chemical determination of pepsin by histological investigation of the gastric mucosa and found no granules in the chief cells until two weeks after birth.

HAMMARSTEN (1874) found the gastric mucosa of the cat to be poor in pepsin during the first week and rich after ten days. Sewall (1878) could demonstrate no pepsin in this species of animal prior to birth. Toldt (1880) found that the differentiation of cells in the main gastric glands was not complete until about a week after birth—a histological observation in good agreement with Hammarsten's chemical findings.

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In the rabbit no pepsin is found immediately after birth (Wolffhügel 1876) but is fairly abundant two weeks later (Hammarsten 1874).

Sheep were investigated in series at close intervals by $s_{\rm E}$ -wall (1878). He showed that differentiation of the chief cells had begun at a foetal length of 14 cm (mature foetus = 50 cm) and had progressed considerably in embryos 19 cm long, in which age group peptic activity of the gastric mucosa could be demonstrated by chemical methods.

In the bovine gastric mucosa, peptic activity could be demonstrated as early as in the third embryonic month (Morriggia 1876, Grützner 1875, Langendorff 1879).

In the pig, Langendorff (1879) could find no peptic activity in embryos just before term.

In the rat, he found pepsin to be present immediately before birth.

As is seen from the above survey, the gastric mucosa of different animals shows no uniformity as to the development of peptic capacity.

It is evident from the foregoing survey of the literature that the development of the foetal gastric mucosa in man has been studied to such a limited extent that no conclusions can be drawn with respect to the peptic activity of the premature infant.

For the following reasons the author has investigated a new fairly large material (70 cases):

- The material of previous investigations on man consists of only a small number of cases, especially in the age group of greatest importance here — the premature — about which conclusions have often been drawn from a single case.
- The material from man in earlier investigations has often been primarily defective due to a long interval between death and preparation.

- 3. The majority of investigations date from a time when methods of examination were unreliable. For this reason probably such an important factor as the granules of the chief cells was not considered in discussing the maturity of these cells. The chemical methods used were qualitative or only roughly quantitative.
- Because of the great variations from species to species the results of fairly detailed investigations on animals permit of no conclusions concerning the situation in man.
- Infants have not hitherto been examined simultaneously both by histological and by quantitative chemical methods.

The Writer's Investigations.

In determining the peptic and tryptic activity, post mortem material was used. Originally the writer intended to supplement the investigations by analyzing the enzymatic activity of gastric and pancreatic juice from clinical material, but preliminary determinations showed that in the case of prematures the sources of error in determining enzymatic activity in clinical material were of such a degree of magnitude as to preclude this kind of investigation. A further opportunity of throwing light on the enzymes of premature infants is given by metabolism experiments. Such experiments in which the writer is participating are in progress at Sachs' Hospital for Children and will be dealt with in a later communication.

Material.

The investigations were mainly carried out on human material and only to a very limited extent on animals (rat, cat, rabbit). According to the literature and the present writer's findings, the development of the enzyme-producing system in the digestive tract of different animals varies from species to species. Since the interest here is focused on the pepsin and trypsin-producing capacity of the premature infant, and since conclusions drawn from animals cannot in this respect be applied to man, investigations on animals were discontinued at an early stage.

The writer's histological material comprised 70 cases¹ of which 47 were premature i. e. had a weight at birth under 2 500 g. The material was thus considerably larger than that of any earlier investigation. Keene & Hewer examined 13 cases, the largest number hitherto mentioned in the literature. Furthermore, the material especially covers the important group of the viable premature cases. The maturity of the gastric mucosa in general and the peptic cells (chief cells) in particular was studied. In 30 cases the peptic activity of the gastric mucosa was determined chemically. Six of the latter cases were not included in the histological material. An analogous examination of the pancreas was made (p. 49).

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Table II. Gastric Material Studied Histologically.

The Cases Arranged in Groups According to Weight at Birth.

Weight at Birth, g	No. of Cases
< 1 000	7
₹ 1 000 < 1 500	18
₹ 1 500 < 2 000	16
₹ 2 000 < 2 500	6
₹ 2 500 < 3 000	5
₹ 3 000	18
	70

The material was obtained from the Sachs' Hospital for Children and from various maternity hospitals in Stockholm (Södersjukhuset, Karolinska sjukhuset and Allmänna Barnbördshuset). Autopsy material was used. It was obtained as early as 1—1.5 hours after death with the exception of two cases (Nos. 18 and 71) and was fixed immediately. In some cases, when the writer happened to be present at the hospital, the preparation of the material was started as early as half an hour after death. The writer preferred to prepare the material personally and thus

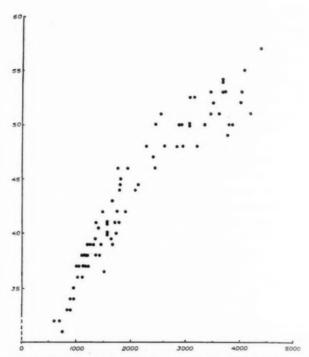
¹ The material originally comprised 101 cases but 31 of them were discarded since study of the case records revealed that either the infant or its mother had suffered from some severe disease.

ensure that all cases were treated uniformly and that pathological cases were discarded, rather than to obtain somewhat earlier fixation by relying on the help of different assistants thus risking a lack of uniformity in the method. Moreover, the interval of one to one and a half hours is relatively short since the body temperature of such small infants after death rapidly falls to that of the surroundings, thus considerably retarding the process of autolysis. Cases of intrauterine death were not included in the material if the infant had been dead more than half an hour before parturition.

The material was subdivided into weight-groups as in Table II. It will be seen that half of the material belongs to the weight-groups between 1 000 and 2 000 g. Thus the main part of the premature cases falls within those interesting groups in which medical therapy really appears to be of value in combating the difficulties of the neonatal phase. The group of 2 000 to 2 500 g contains fewer cases. The limit between full term and prematurity was drawn as is usual at 2 500 g. Two infants with a birth-weight of 2 440 and 2 270 g respectively — each one with its full-term twin — were evidently born at term despite a lower weight.

The material, as is evident from Fig. 1, shows a good correlation between body length and weight at birth. The weight is usually taken as a measure of the degree of prematurity. Body length is, however, a better measure of foetal age, and as it is of importance in this work to correlate the proteolytic capacity of the cases to their foetal age a classification of the cases into, age groups on the basis of body length at birth has likewise been made. Table III gives the cases classified into groups according to body length and approximative foetal age. As is usual in clinical practice, it has been assumed that the foetus grows 5 cm in length during each of the last five foetal months. According to this classification the main part of the premature cases were from the 8th and 9th month. A classification on the basis of the calculated date for parturition likewise shows that the main part of these cases were from this period (Table IV).

^{2 - 48619} Birgitta Werner



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Fig. 1. Diagram of the Correlation between Weight and Length of all the Infants examined. Abscissa: Weight in g. Ordinate: Length in cm.

The postnatal age (Table V) varied from 0 hours to one week, with the exception of one full-term infant, which survived for three weeks. The majority of cases lived for about 24 hours. Some infants died during parturition. These cases are of particular value in estimating the extent to which food in the stomach or the administration of drugs may have influenced the condition of the gastric mucosa.

The material thus consists chiefly of cases from the first post-natal days. This should be sufficient, since the object of the investigation was to study the stage of development of the proteolytic enzyme system in premature and full-term infants during just this time. It would have been interesting to make comparative studies at somewhat later stages as well. This was, nevertheless, not done mainly because so many factors make it difficult to perform a post-mortem examination on a somewhat older child as early as necessary.¹

Table III. Gastric material Studied Histologically.

The Cases Arranged in Groups According to Length at Birth and Approximative Foetal Age.

Length at Birth, em	Approximative Foetal Age	No. of Case	
5 30 < 35	Born in 7th foetal month	6	
₹ 35 < 40	» » 8th » »	19	
₹ 40 < 45	* * 9th * *	15	
₹ 45 < 50 · · · · · · · · · · · · · · · · · ·	» » 10th » »	8	
₹ 50	at Term	22	
		70	

TABLE IV. Gastric Material Studied Histologically.

The Premature Cases Arranged in Age-Groups on basis of the Date Calculated for Parturition.

Degree of Debility										No. of Cases				
Born	in	6th	foetal	month							*	*		1
10	à	7th	0	18										4
0	19	8th		0		×	,				*			17
9	19	9th	10	33						*				11
19	13	10th		13			*			*				0
													-	33 ²

 $^{^1}$ Two older infants (4 $^1/_2$ months and 1 year of age respectively) have nevertheless been examined (p. 29) so as to get an idea of the tendency in the development.

² Reliable information was not available in the other premature cases.

Table V. Gastric Material Studied Histologically.

Time of Survival of the Infants.

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	No. of Cases					
Time of Survival	Premature 1	Full-tern				
0—a few minutes	5	10				
< 24 hours	23	2				
₹24 < 48 ·	11	4				
2-3 days	6	5				
c:a 1 week	2	1				
c:a 3 weeks	0	1				
	47	23				
	Total 70					

Table VI. Gastric Material Studied Histologically.

Causes of Death of the Infants.

	No. of	Cases
Cause of Death	Premature 1	Full-tern
Congenital debility (only)	17	
Intervention during parturition	3	43
Pulmonary atelectasis	12	3
Intracranial haemorrhage	8	3
Intracranial haemorrhage + Pulmonary ate-		
lectasis	4	5
Bronchopneumonia	1	1
Congenital heart disease	0	3
Intrauterine asphyxia	1	3
Erythroblastosis foetalis	0	1
Superarenal apoplexy	1	1
	47	23
	Tota	1 70

It was naturally extremely difficult to obtain material to which no objections could be raised regarding the normality of the digestive tract. An ideal material should consist only of

 $^{^{1}}$ Birth-weight < 2500 g.

cases that died owing to intervention during labour. The writer was, however, unable, despite considerable efforts, to obtain more than a few such cases, which can be regarded as controls. Since it was not possible to obtain completely homogeneous material, the writer endeavoured to compensate this lack by comparing premature cases in which the cause of death was another than debility alone with corresponding full-term cases. Table VI shows the cause of death in the various cases.

It can be objected that two cases (1 full-term and 1 premature) with infectious diseases are included in the material. The cases, however, showed no clinical symptoms. The infection, bronchopneumonia, was observed first on post-mortem examination and then proved to have been extremely mild in character. The writer had originally considered excluding them, but investigation of the gastric tract had already been started when the infection was discovered in the course of the routine post-mortem examination, and as it was found that the examined full-term case suffering from infection did not deviate from the normal full-term cases as regards the rich granule content of the chief cells normally present in these cases (p. 29), both were retained.

Sources of error in the material.

It is impossible in biological studies, particularly on human material, to avoid certain sources of error. Those of particular significance in the present study are as follows:

- 1. The material was not absolutely fresh.
- Owing to the varying causes of death, the material was not homogeneous.
- The survival time varied. External factors, such as the administration of food and drugs, may therefore have influenced the condition of the gastric mucosa.

1. The material was not absolutely fresh.

Preparation of the material could not be begun until some time after death of the infants and this source of error was therefore unavoidable. Had the subjects been adults, this error would have

been very serious, since the high content of hydrochloric acid and pepsin in the stomach, as well as a fairly high body temperature during the first hours after death, would have favoured disintegration of the gastric mucosa. According to MILLER (1941) and others, very little or no hydrochloric acid is, however, present a premature infant and the peptic activity would therefore post mortem be inconsiderable. Since considerably more hydrochlories acid is usually present in full-term infants, autodigestion of gastric mucosa could, of course, take place. This would, however, diminish the amount of pepsinogen granules and thereby total to decrease rather than increase the difference found (p. 33) between the premature and the full-term infants. Since the writer, despite this fact, found an unmistakable difference between these two types of newborn infants, this source of error does not appear to have been of decisive importance. As more tioned previously, disintegration is considerably retarded in newborn infants since, due to their small weight, the body temperature falls rapidly after death. That this fact is of importance can easily be demonstrated by comparing the gastrie mucosa of a rat kept for 1.5 hours after death at a temperature of 15° C with that of one kept for the same time at 35° C. In the former case the mucosa is well preserved and in the latter disintegrated.

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2. The material was not homogeneous as regards the cause of death.

Human material is almost unavoidably heterogeneous in this respect. The uniformity of the results throughout the investigation nevertheless indicates that this source of error can have been only of minor importance. Moreover, in each group of diagnosis full-term cases were available for comparison with the premature (Table VI).

3. External factors, such as the administration of food and drugs. might have influenced the condition of the gastric mucosa.

According to earlier writers, the digestion of food causes a decrease in the amount of granules of the gastric mucosa.

Nevertheless there is no reason to suppose that the chief cells are completely emptied before the production of more pepsinogen granules starts. Several writers, Sewall (1878), Langley (1879), GREENWOOD (1882), NOLL & SOKOLOFF (1905), DI CHRISTINA (1908), BABKIN (1944), have namely pointed out that the simulation caused by the ingestion of food decreases the number of granules in the gastric mucosa, but by no means causes them to disappear completely. In this respect normal stimulation differs from artificial with pilocarpine or electrical stimulation of the vagus nerve. The present writer investigated the gastric mucosa of young rabbits and rats both after starvation and after administration of food and found that although there was a decrease in granule content after meals, it was still considerable. In the writer's human material the difference between the amount of granules in premature and full-term infants was so considerable (p. 31) that it should completely eclipse any variations due to different phases of digestion. A comparison of full-term cases to which food was administered with those which received no food revealed no marked difference in the amount of granules, nor did the administration of drugs appear to have had any effect in this respect. Cases in which death had occurred during parturition were used as controls.

Material from animals.

The writer's animal material was collected from rats, rabbits and cats. The writer, as did earlier workers, found varying conditions in different species of animals as regards the granules of the chief cells of the gastrie mucosa. The rat showed granules at birth with a considerable increase during the first days of life. No granules of the chief cells were found in newborn rabbits, nor were any demonstrable in the cat up to the 6th day of life.

As mentioned previously, both starving and digesting animals were examined. A difference, though not a marked one, in the amount of granules was observed.

Preparation of the material.

Partial autopsy was performed one to one and a half hours after death. The stomach, duodenum and that part of the small

intestine immediately following it were excised. The pancreas and intestine were dissected from the stomach and duodenum. (For further details of the preparation of the pancreas see p. 54.) The stomach was opened along the greater curvature by an incision prolonged through the duodenum. The stomach was usually empty. The mucus covering the gastric membrane was wiped off with paper tissue but in no case was the membrane washed. All cases showing any pathological conditions in the digestive tract, such as an intestine abnormally filled with gas, discoloured ventricular content or punctate haemorrhages in the gastric mucous membrane were discarded. The specimens examined all showed macroscopically well preserved mucosa, pale greyish-red and with normal folds.

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The specimens were stretched on a cork sheet and fixed to it with glass nails through the margin of the gastric wall. Since in the chemical method used in this investigation the peptic activity was determined per unit surface area of the mucosa from the body of the stomach, it was necessary in the cases examined by the chemical method to excise pieces of the gastric mucosa of a known surface area. Therefore the stomach wall was stretched on the cork sheet to just the extent necessary to flatten the folds of the mucosa. One or several pieces were stamped out from the body of the stomach with a hollow cylindrical silver-steel corkbore of known diameter. (See p. 36 for the further chemical treatment of the excised samples.) The remainder of the mucosa. as well as the whole stomach, in those cases in which only histological examination was carried out, was treated as follows:

Histological Treatment of the Gastric Mucosa. Fixation and staining.

After the stomach wall had been stretched on the cork sheet it was fixed according to Regaud's method. The fixation fluid consisted of a 3 per cent aqueous solution of potassium bichromate and a 40 per cent solution of formaldehyde in the proportion of 4:1, the solutions being mixed immediately before use. Since acid dissolves the granules in the cells, the formaldehyde

was neutralized with calcium carbonate. In order to obtain well preserved granules, it is essential to mix the fluids immediately before use. The preparation remained in the fixing solution for 4 days, the fluid being changed daily. It was then transferred to a 3 per cent solution of potassium bichromate with a change of the solution every 48 hours. Fixation took place in a dark vessel. The preparation was then washed for 24 hours in running water and dehydrated in rising concentrations of alcohol. It was embedded at 56° C in paraffin after rapid passage through methyl benzoate, benzene and benzene—paraffin.

Bowie & Vineberg achieved excellent results in their experiments using this fixation method. The present writer tested the method on the gastric mucous membrane of human adults and found it satisfactory. Preservation and staining of the zymogen granules have earlier caused considerable difficulties, since the majority of fixatives dissolve the granules. The writer was only interested in finding a reliable method for the investigation of a clinical material and not in testing various techniques used previously, often with unsatisfactory results. No discussion of such methods will therefore be entered into here.

The preparations were cut into sections as thick as $10\,\mu$ in order to make it easier to observe the granules in the less rich sections.

The sections were stained according to the method described by Bowie (1936). He used crystal violet and orange G to stain the granules of the chief cells in contrast to other tissues. The present writer used the same combination of stains, i. e. crystal violet (Aktiengesellschaft für Anilinfabrikation, Berlin) and orange G (G. T. Gurr, London).

Stock staining solution: 2 g of crystal violet were dissolved in 500 cc of distilled water and 1 g of orange G in 250 cc of distilled water. Both solutions were filtered. The crystal violet solution was then added to the orange G solution in such a quantity that a few drops of the mixture on a filter paper gave a violet blot, crystal violet being added as long as this violet blot was surrounded by a yellow zone. When the mixture was allowed to stand a precipitate soon formed. This was filtered off and

dried to a powder. The stock solution was prepared by dissolving 0.1 g of powder in 10 cc of 95 per cent alcohol. It was found possible to keep this stock solution for several months without its deterioration.

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Staining solution: 0.8 ec of the stock staining solution was added to 50 ec of 20 per cent alcohol prepared with newly distilled water.

Staining and differentiation: The sections were passed through xylene to absolute alcohol and down to 50 per cent alcohol and then transferred directly to the staining solution in which they remained for 24 hours. The slides were then removed and dried off quickly around the section and blotted once only under three layers of smooth filter paper. The paper was carefully lifted from the slide and the section for differentiation at once covered with a few drops of clove oil diluted with an equal volume of xylene. The differentiation usually took 30—60 minutes. When it was complete, the sections were passed through several baths of xylene and benzene and mounted in benzene balsam, which was allowed to harden at room temperature, since according to Bowie the stain fades in heat.

Staining results: The granules of the chief cells stained intensely dark violet, the surface epithelium somewhat lighter violet, the red corpuscles brick red and the white corpuscles dark violet. The remaining tissue stained pale reddish-yellow. The granules of the chief cells thus contrasted excellently against it. (Plate I.)

On account of its morphology, the surface epithelium cannot confuse the picture, despite its similarity in colour. In black and white photographs of the sections at a low magnification, however, the blood corpuscles can lead to some confusion since they. like the granules, can be assembled in groups basally in the mucous membrane. In the slides, however, there is naturally no difficulty in this respect.

Bowie emphasized that the preparation should be fresh and of suitable thickness for fixation in order to obtain a satisfactory staining afterwards. Both the groups to be compared in the present writer's investigations were treated similarly, and since the thinness of the tissue walls was ideal for fixation, the conditions for staining should have been favourable. Bowie fixed the sections to the object glass with gelatin. The present writer used egg-white and glycerol without inconvenience. Since it was not possible to obtain natural clove oil, eugenol was used instead. The eugenol obtainable proved to contain impurities which caused profuse diffusion of the stain during differentiation, and it was therefore necessary to purify it by repeated distillation before use.

The secretion of the hydrochloric acid in the stomach of the newborn seems to be fairly well studied especially after Miller's (1941) largescale investigation on full-term and premature infants. This and other investigations make it clear that the premature infants exhibit achlorhydria in a large percentage of cases. In ten cases Miller studied the histological picture of the gastric mucosa of full-term and premature infants with special attention to the parietal cells. In these cases he found that the parietal cells were scantily represented in infants under 2000 g and that their number increased with the weight of the infant, the gastric mucosa of infants weighing 3 000 g being rich in these cells. The writer has in the present work cursorily studied the parietal cells and found a situation in good agreement with Miller's results. The parietal cells were at first studied in slides stained with haemalum Congo red in which the chief cells stain blue and the parietal cells reddish brown. Since the latter were, however, distinctly seen (Figs. 6, 10, 21, 24) even in slides stained with orange G crystal violet they were later studied only in these slides.

Sources of error in the histological technique.

As the premature cases were prepared identically with the full-term ones the sources of error should have been the same in the two groups compared and there should consequently be no variations in the results due to the technique. It should be evident from the fairly detailed review of earlier investigations that it is possible to stain satisfactorily the granules which are intimately—either by being the proenzyme or in some other way—connected with pepsin. Bowie's and Vineberg's experiments (p. 8) were of particular significance in this respect. It is not, however, self-evident that other substances, such as the

intrinsic factor, rennin, lipase and urease, in addition to pepsiul have no relation to the granules stained.

. The intrinsic factor can be disregarded, since it occurs in the pig in the mucosa of the pylorus, although this has no granules stainable with the method used here.

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The presence of rennin as a special enzyme in the stomach of the calf must nowadays be considered as established. TAUBER & KLEINER (1932) were able to isolate in calves a highly active remain preparation entirely free from pepsin. It has not, however, been possible in man nor in a number of other mammals to differentiate the carrier of the rennin principle from pepsin. If two different enzymes were present it should be possible to separate them by some of the methods used on calves (Hammarsten 1874, 1908, 1911, 1915, 1922, RAKOCZY 1910). Since Northrop and collaborators (Northrop, Kunitz and Herriott 1948) demonstrated that crystalline pepsin also has a considerable rennin effect, it is most probable that the rennin activity in these mammals is due to pepsin (Holter and Andersen 1934). Andersen (1935) was unable to demonstrate in infants any particular enzyme other than pepsin with a rennin effect. On these grounds it should therefore be possible to eliminate rennin in a discussion concerning the granules of the chief cells.

According to the majority of workers, Ibrahim (1909), Keene & Hewer (1929), Klumpp & Neale (1930), Levine & Gordon (1942), lipase is present in the stomach of newborn infants, but its site of production does not coincide with that of pepsin. Glick (1934) using Linderstrøm-Lang's section cutting technique, demonstrated that lipase occurs particularly in the superficial area of the mucous membrane of the entire stomach. On comparing various regions of the stomach, it was found that the region in which the chief cells are most numerous contained least lipase.

With the same method, the presence of urease in the stomach was also demonstrated, but only in the most superficial layers of the mucous membrane (Linderstrøm-Lang and Ohlsen 1936. Fitzgerald 1946).

It can therefore be concluded that the relation between pepsin and the granules of the chief cells is a specific one.

Histological results.

Microscopical examination revealed no pathological conditions in the stomach in any of the cases included in this material.

Cases with a birth-weight over 3 000 g.

Since the full-term cases represent normal conditions, it is most suitable to begin with them when describing the gastric mucous membrane in various age groups. Cases with a birthweight between 2 500 and 3 000 g which may or may not be full-term are described after the premature.

The full-term mucous membrane was well developed with narrow pits and in the body of the stomach closely spaced glandular tubules which reached the base of the mucous membrane. There was differentiation of the cells, with a deeply staining superficial epithelium and well marked chief and parietal cells. The maturity of the glandular mucosa was such that the chief cells lying most basally around the blind ends were filled with pepsinogen granules, which stained dark violet. Each gland had a small group of cells containing granules. (Figs. 5, 7, 8, 12, 13, 18, 20, 23 and 26.)

At low magnification a typical picture of the preparation was obtained on microscopic examination: in the deepest part of the mucosa a marked border of violet granules was seen to contrast against the light pink colour of the remaining tissue (Plate I). The chief cells higher up in the glandular tubule, counted from its blind end, showed no granules. They differed here from the parietal cells in being small and dark.

Specimens taken from two older full-term infants (aged 4 months 2 weeks and 12 months respectively showed a picture intermediate to newborn full-term and adult gastric mucosa. In the latter the granular zone occupies approximately three-fourths of the cross section of the mucous membrane. (Figs. 2 and 3.)

It is of interest to point out that as is evident from the description of the cases (p. 66) there were very few deviations from the normal picture described here. The granules in the mucosa were less apparent in some areas but areas rich in them were always found. The results could not have been so uniform

had the deficiencies in the material due to variations of the survival time, administration of food and drugs, general condition and cause of death had any decisive influence on the amount of granules of the chief cells.

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Cases with a birth-weight from 1000 to 2000 g.

The smallest infants were from the beginning of the 8th, and the heaviest from the 9th foetal month. In the youngest infants the mucous membrane was strikingly immature (Fig. 24). It was then, the pits were wide and the glandular tubules short and widely spaced. During the 8th and 9th foetal months the mucosa became more mature in character. The glands became longer and more closely spaced. Even in the youngest infants there was differentiation of the glandular cells into parietal and chief cells and the surface epithelium stained deeply violet (Plate II). The parietal cells were large and light, situated both in the line of the chief cells and, in older infants, behind them in relation to the lumen. The chief cells were smaller and darker and situated at the lumen of the gland.

As regards the granules of the chief cells, there was no reason to subdivide the cases into age groups, since the granules were as scarce in the 9th as they were in the beginning of the 8th foetal month. At low magnification microscopic examination of a vertical section of the mucosa revealed no granules in any of the cases. If the basal region of the mucosa was examined closely at high magnification, a few. often small, typically stainable granules were observed in some scattered cells at the base of the glands (see description of the cases p. 66). In several (24) of the preparations the writer found no granules. It could be expected that the latter preparations represented only the youngest cases in the group. This was, however, not the case since gastric mucosa from infants just under the limit of 2 000 g sometimes showed no granules. Plate II shows a vertical section of a mucous membrane from this group. It is not typical for the group as a whole as regards its semi-macroscopic appearance, since it is an extremely primitive one. The older

cases had usually a somewhat more mature appearance (Figs. 4, 10, 25.) As regards the granules it is, however, representative since all through the group these were so scanty that they were only visible at high magnification. Granules do not therefore increase in amount with increasing age in this group to such an extent that younger and older cases can be distinguished.

The difference between full-term cases and those discussed here is very considerable as is seen on comparison between Colour Plates I and II or on comparison of for instance Figs. 5, 7 and 12 with 4, 6 and 14. The writer's material thus indicates that the development in maturity of the chief cells is very slow during the foetal months from which a large and important group of premature infants derive.

Cases with a birth-weight from 2000 to 2500 g.

In the group of infants with a weight at birth over 2000 and up to 2500 g, i. e. cases from the 9th and 10th foetal months there was, contrarily to what could be expected, no considerable increase in the amount of granules. The coarser structure of the mucosa had a practically mature appearance with closely spaced glands (Figs. 9, 17). The development in this respect was entirely in agreement with the observations made by Scott (p. 13), i.e. that there is a particularly large increase in the number of glands during the first third of the 10th foetal month. The increase in the amount of granules of the chief cells was however rather insignificant. The granule-containing cells occurred at closer intervals along the basal line of the mucosa, but this was probably only due to the increased number of glands. The number of granules in each cell was still small. The larger number of cells containing granules nevertheless implied that the mucous membrane taken as a whole was somewhat richer in granules. In this group the gastric mucosa held more numerous parietal cells than in the foregoing group.

Apparent exceptions in this group were two infants weighing 2 440 and 2 270 g respectively (Cases No 6 and 36) which despite their low weight had a gastric mucous membrane rich in

pepsinogen granules (Fig. 15). These infants were, however, full-term, since each had a twin weighing more than $3\,000~{\rm g}.$

Cases with a birth-weight under 1000 g.

In the few preparations available from infants weighing less than 1000 g (Fig. 11) the gastric mucous membrane was thin and poorly developed as regards glands. The writer observed a few granules in solitary cells in one of these cases, but none in the others.

Cases with a birth-weight from 2500 to 3000 g.

In the group of infants weighing between 2 500 and 3 000 g at birth (Fig. 16) there were transition cases with numerous pepsinogen granules as well as cases in which these were scanty. Parietal cells were present in still greater numbers than in the previous group.

Discussion of the results.

As can be seen from the foregoing discussion and from the photographs, the difference between premature and full-term infants as regards the granule content of the chief cells in the gastric mucosa is so marked that a mathematical expression of this difference seems to be quite superfluous.

The writer's material indicates that though it is possible that the formation of pepsinogen granules in the chief cells starts at an early stage of foetal life, then it progresses so slowly that it is not possible to grade the maturity of the chief cells in cases from the beginning of the 8th to the beginning of the 10th foetal month. The granule formation then accelerates considerably during the 10th foetal month.

The writer, as did Miller (1941), found but few parietal cells in the younger premature infants, and an increase in number with increasing age. These cells were, however, only investigated cursorily by the writer in the slides made for the work on pepsin. No conclusions regarding their functional capacity were therefore drawn.

These findings are of interest because, even if the fact that the stomach of a premature infant is also in a premature con-

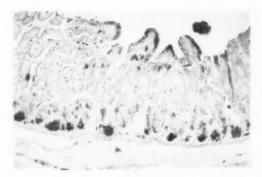


Plate I. Gastric mucosa from a full-term infant. Weight at birth 3340 g. Death 24 hours after birth due to bronchopneumonia. In the basal part of the mucosa a border of cells containing violet pepsinogen granules.

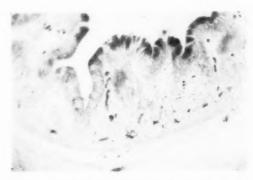


Plate 11. Gastric mucosa from a premature infant. Weight at birth 1560 g. Death 24 hours after birth due to congenital debility. In the basal part of the mucosa no granules are to be seen.

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Fig.]. Gastric mucosa from an adult showing the amount of pepsinogen granules. These occupy more than three-fourths of the vertical section. Enlargement 70 \times

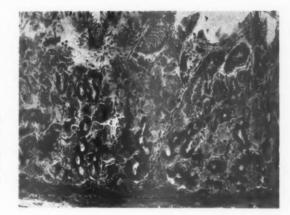


Fig. 3. Gastric mucosa from a full-term infant 4 months, 2 weeks of age.

The border of pepsinogen granules is much more marked than in newborn full-term infants.

Enlargement 188 ×

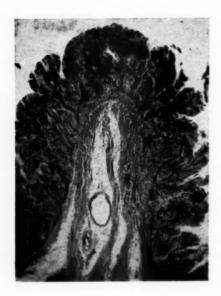


Fig. 4. Case No 19.

Birth-weight 1930 g.

Premature gastric mucosa.

Some pepsinogen granules in recher many chief cells but not discernib in the photograph.

Enlargement 125 ×

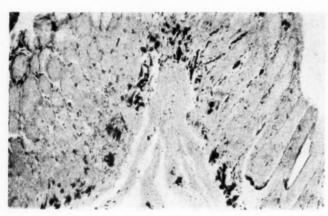


Fig. 5.
Case No 44.
Birth-weight 4 000 g.
Full-term gastric mucosa.
A marked border of pepsinogen granules.
Enlargement 188 ×





Propature gastric mucosa.

Ne epsinogen granules dis-

ce) ble.

En rgement $188 \times$

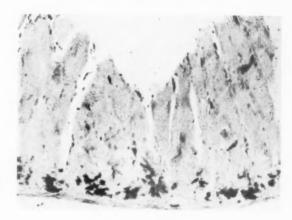


Fig. 7. Case No 33.
Birth-weight 3 680 g.
Full-term gastric mucosa.
A marked border of pepsinogen granules.
Enlargement 188 ×

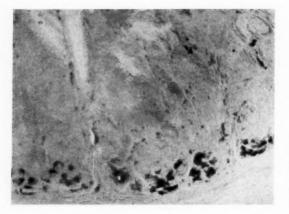


Fig. 8. Case No 17.
Birth-weight 4 080 g.
Full-term gastric mucos
A marked border of psinogen granules.
Enlargement 188 ×

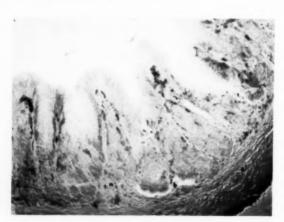
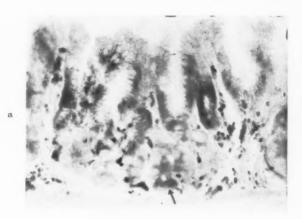


Fig. 9. Case No 58.
Birth-weight 2 120 g.
Premature gastric mucosa.
A few groups of pepsinogen granules not discernible in the photograph.
Enlargement 188 ×

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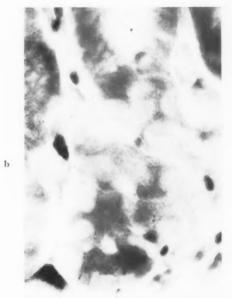


Fig. 10. Case No 54. Birth-weight 1790 g. Premature gastric mucosa. Small groups of granule-containing cells. Enlargement a $188 \times$, b $625 \times$

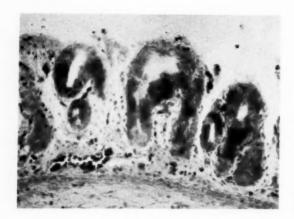


Fig. 11. Case No 60,
Birth-weight 950 g,
Premature gastric mus a.
No pepsinogen granules securible (the black "granles" seen represent bad corpuscles).
Enlargement 188

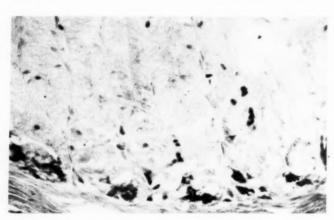


Fig. 12. Case No 1. Birth-weight 3 620 g. Full-term castric mucosa. A marked border of pepsinogen granules, Enlargement 325

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Fi. 13, Case No 66, Bir h-weight 3 790 g, Full-term gastric mucosa. A marked border of pepsinogen granules. Enlargement 325 ×

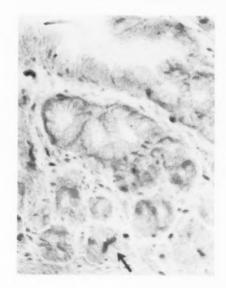


Fig. 14. Case No 63.
Birth-weight 1 660 g.
Premature gastric mucosa.
In two cells pepsinogen granules discernible.
Enlargement 325 s.

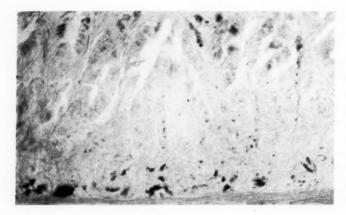


Fig. 15.
Case No 6
Birth-weigl
2 440 g.
Gastric mu sa
from a from twin
A marked arder of pep 10gen gran 8.
Enlargeme
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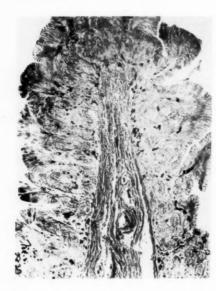


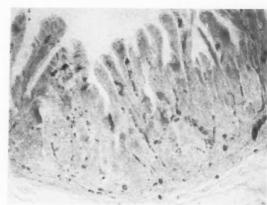
Fig. 16. Case No 24.

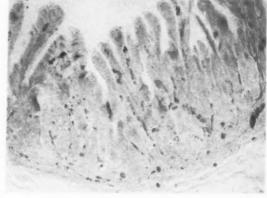
Birth-weight 2 830 g.

Gastric mucosa from an infant born 2 weeks before calculated time.

Some pepsinogen granules in rather closely placed groups (the arrows) not clearly discernible in the photograph.

Enlargement 125 ×





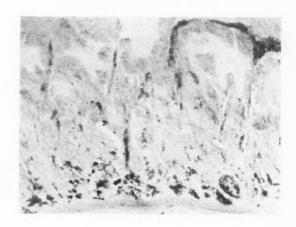


Fig. 18. Case No 37. Birth-weight > 3000 g. Full-term gastrie mucosa. A marked border of pepsinogen granules. Enlargement 188 ×

Fi. 17. Case No 5. Bi a-weight 2070 g. Pi nature gastric mucosa. Sp se pepsinogen granules no liseernible in the photo-

En rgement 188 ×

gro h.

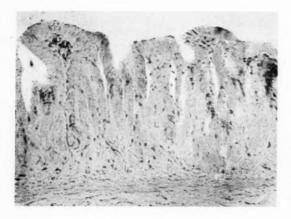


Fig. 19. Case No 70,
Birth-weight 1250 g,
Premature gastric mu a,
Some pepsinogen gra as
in single chief cells.
Enlargement 188 ×



Fig. 20. Case No 29.
Birth-weight 3 450 g.
Full-term gastric mursa.
A marked border of pepsinogen granules.
Enlargement 188 ×

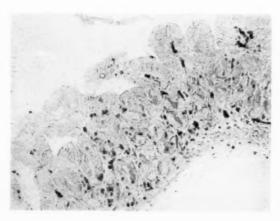


Fig. 21. Case No 49.
Birth-weight 1 020 g.
Premature gastric mucosa.
No pepsinogen granules discernible.
Enlargement 188

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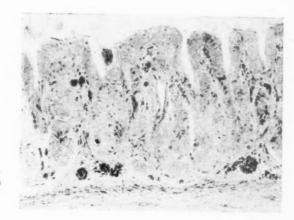


Fig. !2. Case No 64.

Bir - weight 1150 g.

Prenature gastric mucosa.

Some pepsinogen granules in single chief cells.

Enlargement 188 ×

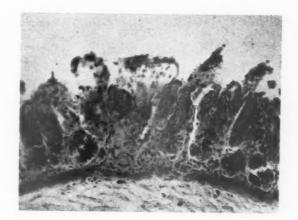


Fig. 23. Case No 61.
Birth-weight 3 450 g.
Full-term gastric mucosa.
A marked border of pepsinogen granules.
Enlargement 188

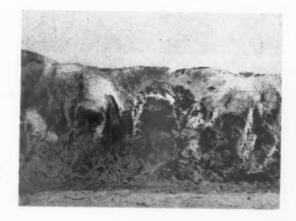


Fig. 24. Case No 68, Birth-weight 1 310 g. Premature gastric mucosa, No pepsinogen granules discernible, Enlargement 188 ×



Fig. 25. Case No 14.
Birth-weight 1 695 g.
Premature gastric mucosa.
Small groups of pepsinogen granul

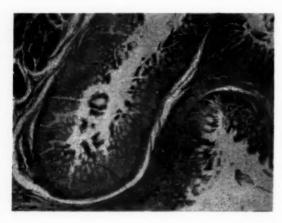


Fig. 26. Case No 45.
Birtn-weight 3 070 g.
Full-term gastric mucosa.
A marked border of pepsinogen granules runs along the basal line of the mucous membrane.
Enlargement 70 ×



Fig 27. Case No 68,

 $P_{\rm Fe}$ -ature gastric mucosa $f_{\rm FO}$ - an infant with a weight

of 310 g.

Mi us surface cells stained wit Schiff's reagent after treament with periodic

Enlargement 188 ×

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dition is not surprising, the immaturity of the stomach late in fortal life is far greater than would appear likely from the degree of prematurity of the infant.

Chemical Determination of Peptic Activity in Extracts from the Gastric Mucosa.

As is evident from the discussion of the histological results, a marked difference was found in the amount of pepsinogen granules of full-term and premature infants. The probability that this difference represents a corresponding difference in the ability of these two groups of infants to digest protein is well supported by analyses of the peptic activity in a number of the cases studied histologically.

TABLE VII. Gastric Material Studied Chemically.

The Cases Arranged in Groups According to Weight, Length and Approximative Foetal Age.

Weight at Birth, g	No. of Cases
< 1 000	5
₹ 1 000 < 1 500	7
$ \bar{>} 1500 < 2000 \dots $	
₹ 2 000 < 2 500	. 1
₹ 2 500 < 3 000	2
₹ 3 000	6
	30

Length at	Birth, cm	A	ppi	No. of Cases				
$\equiv 30 < 35$		Born	in	the	7th	foetal	month	4
		39	10-	19	8th	39	i)	9
5 = 40 < 45		>>	.0		9th	9	*	8
545 < 50		33			10th	*		4
₹ 50		**	at	terr	n			5
								30

^{3 - 48619} Birgitta Werner

Table VIII. Gastric Material Studied Chemically.

Time of Survival and Causes of Death.

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TO' A CO	No. of	Cases				
Time of Survival	Premature ¹	Full term				
0 hours	1	1				
< 24 %	13	3				
₹ 24 < 48 hours	3	1				
2—3 days	3	•)				
5 »	1	0				
3 weeks	1	1				
	22	8				
	Tota	1 30				
	No. of	No. of Cases				
Cause of Death	Premature ¹	Full-term				
Congenital debility (only)	9					
Intervention during parturition	1	0				
Pulmonary atelectasis	5	1				
Intracranial haemorrhage	5	4				
Pulmonary atelectasis + Intracranial haemor-						
rhage	0	.1				
Bronchopneumonia	1	0				
Congenital heart disease	0	1				
Intrauterine asphyxia	0	1				
	1	0				
Suprarenal apoplexy						
Suprarenal apoplexy	22	8				

These analyses were for several reasons started later than the histological investigation and thus only 24 cases out of the 70 cases studied histologically were examined. Six additional cases were studied only chemically. 22 out of the total 30 cases had a birthweight under 2 500 g.

The youngest infant had a birth-weight of 700 g. The majority of the premature infants belonged to the 8th and 9th foetal months and had a birth-weight between 1 600 and 1 700 g. Three

¹ Birth-weight < 2 500 g.

cases with a birth-weight between 2 000 g and 3 000 g are included in this material. Of these, one weighed 2 120 g at birth, had a body length of 44.5 cm and was born eight weeks before term, the second, 2 600 g, 48 cm long, born five weeks before term and the third, 2 940 g, 48 cm long and born two weeks before term. (Table VII.)

The time of survival and causes of death are seen in Table VIII. The survival time varied between 0 hours and 1 week with the exception of two cases, one premature and one full-term, both of whom lived for three weeks.

In the chemical studies the peptic activity was determined per unit surface area of the mucosa from the body of the stomach.

Preparation of the Material.

As described earlier (p. 24), the stomach was opened and fixed to a cork sheet. The mucous layer covering the inner surface of the mucous membrane was wiped off with paper tissue and one or several pieces of the gastric mucosa of a known surface area stamped out from the wall of the stomach.

In determining the actual surface area of the excised samples it was necessary to stamp out the samples from a mucosa in which the folds had been completely flattened but not excessively stretched. The stomach wall was therefore stretched to just the extent necessary to flatten the folds in the mucosa. This was easy in the premature but somewhat more difficult in the full-term cases, where the muscular layer of the gastric wall was more developed. In the latter a certain degree of excessive stretching was preferred to insufficient flattening of the folds, since excessive stretching would decrease rather than increase the difference found (p. 43) between the two groups of infants compared.

In a number of cases two proximal samples were taken from the body of the same stomach and the peptic activity determined in extracts from each of them. Results from the corresponding samples given in Table IX indicated that the surface area could be determined fairly accurately.

TABLE IX.

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Comparison in Some Cases of the Peptic Activity in the Extracts from Two Proximal Samples (I and II) of the Gastric Mucosa from the Same Stomach, The Peptic Activity is Estimated by the Method Described on Page 38 and Expressed in Milliequivalents $\times 10^{-6}$ Tyrosine per cc. Trichloracetic wind Filtrate.

Case No.								Sample of Mucosa excised												
										1	II									
65							*	*											16.4	16.0
66															*				20.3	19.7
67				. ,							*								19.8	*******
68		ė									,					. ,			12.1	11.4
69																			14.6	14.5
70						*	*												10.5	10.8
71						*								*					12.2	-
72		*										. ,							9.5	9.6
73																			18.0	-
74													 *						11.9	10.6
75																			2.2	3.0
76																			0.7	0.9

The excised samples of mucosa were frozen in liquid air and allowed to thaw at 4° C in order to disrupt the cellular structure, thereby facilitating extraction of the zymogen. 10 cc of $0.1~\mathrm{N}$ hydrochloric acid per 226.8 mm² (= 0.5 cc per 11.34 mm²) surface area of mucosa was then added to the sample and extraction and activation of the pepsinogen allowed to take place, with frequent stirring, at 4° C.

After 48 hours the extraction mixture was centrifuged and the peptic activity determined in a dilution series of the clear supernatant. A dilution series was made since the values found for the peptic activity of the different dilutions must fall on a curve with a characteristic form. An atypical curve would indicate an error at some stage.

The Method used for Determination of Peptic Activity.

The estimations of peptic activity have been made with Anson's colorimetric method (Anson 1938, Northrop 1939).

This method was for several reasons better suited to the requirements of this investigation than the more commonly used titrimetric methods in which the enzymatic activity is measured by the amount of carboxyl or amino groups liberated during digestion of a protein substrate under standard conditions. Thus, for instance, it is evident that in estimating the enzymatic activity in unpurified organ extracts the amount of carboxyl and amino groups liberated will depend not only on the amount of proteinase in the sample to be analyzed but also on the various peptidases that are almost infallibly present in crude extracts and that find an ideal substrate in the proteinase-predigested protein. The amount of carboxyl and amino groups liberated during digestion will therefore be greater than that which can be accounted for by the activity of the proteinase alone. In Anson's method the enzyme solution to be tested is allowed to digest haemoglobin under standard conditions and its activity measured by the amount of those split products that are formed during digestion, and which give a characteristic blue colour with Folin-Ciocalteu's phenol reagent. The colour given by the split products is due chiefly to the tyrosine liberated during digestion and is arbitrarily assumed to depend on this amino acid only. The intensity of the colour is therefore compared with that given by a tyrosine solution of known concentration, and the enzymatic activity expressed by the amount of tyrosine which would give a colour of the same intensity as that given by the split products. In this method such split products as give a blue colour with Folin-Ciocalteu's reagent are formed exclusively by the action of proteinase on protein (Myrbäck & Bamann 1941). Consequently, continued digestion of the proteinase-predigested substrate by peptidases does not increase the colour value of the split products. Contamination with peptidases of the sample to be analyzed for proteinase should therefore have little or no influence on the accuracy with which the proteinase activity can be estimated according to this method.

In this work, where the activity of unpurified enzyme extracts had to be analyzed, some deviations from Anson's method were unavoidable, and a description of the experimental procedure therefore follows.

Preparation of the substrate.

a) Haemoglobin stock solution:

Fresh ox blood was decalcified at the slaughterhouse by the addition of one part of a 3.8 per cent solution of trisodium citrate to four parts blood. After cooling it was brought to the laboratory and centrifuguel. The supernatant plasma and the layer of leucocytes covering the red corpuscles were sucked off and discarded. The red corpuscles were was ind by suspending them in 50 volumes of physiological saline, the saline being removed in a blood separator. The thick mass of washed corpuscles was poured into cellophane tubes, 1 cm in diameter, and dialyzed against running tap water. After 48 hours' dialysis, during which haemolysis took place, the haemoglobin solution was practically free from substances not precipitable by trichloracetic acid, that give a colour reaction with Folin-Ciocalteu's phenol reagent. As the presence of the stroma did not interfere with the procedure at any stage, no attempt was made to remove it. The protein concentration was determined by desiccating a sample of known volume at 105° C and weighing the residue. The value thus found was checked by determining the protein nitrogen by the micro-Kjeldahl method.

The haemoglobin solution was frozen in 50 cc cardboard ice-cream containers and stored at —15° C. The containers were covered to prevent evaporation. The haemoglobin solution could be stored in this condition for months without decomposing. Whenever a new solution of haemoglobin was made, a substrate prepared from it and from the previous solution was found to give the same value when digested with equal amounts of purified pepsin.

b) Substrate:

The substrate was prepared as follows: A container of haemoglobin solution was allowed to thaw and was thereafter diluted to a haemoglobin concentration of 2.5 per cent with redistilled water. The pH was brought to 1.6 by the addition of 0.3 N HCl (3 parts 2.5 per cent haemoglobin solution and 1 part HCl). The haemoglobin substrate could be kept in this condition at 5° C for at least two days without an increase in the blanks.

Procedure in estimating the peptic activity.

Digestion was carried out in thin-walled test tubes, 130×15 mm, placed in a water bath at 30° C for the time of digestion. Preliminary to the actual digestion all test tubes and flasks containing the enzyme solution were kept in an ice-water bath. The

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extract of the gastric mucosa was partly used undiluted and partly after dilution with 0.1 N HCl to 75, 50 and 25 per cent of the original solution. For the different enzyme dilutions, two test tubes - one for the test and one for the blank - were placed in the ice-water bath and 0.5 cc of the corresponding solution pipetted into each of them. The tubes with the enzyme solutions were then transferred one at a time to the water bath, and 2.5 cc of the substrate solution pre-warmed to 30° C immediately added, the time of adding the substrate being noted. The substrate and enzyme solutions were thoroughly mixed with a slender glass rod which was left in the test tube during digestion. The tubes with the blanks remained in the ice-water bath. Exactly 20 minutes after the substrate had been added digestion was discontinued by mixing 5 ce of 0.3 N trichloracetic acid with the digestion mixture. First trichloracetic acid and then substrate was added to the blanks. All tests and blanks were filtered. Munktell's filter paper 00 was used. 5 cc of 0.5 N NaOH and 1.5 cc of Folin-Ciocalteu's phenol reagent (diluted 1:3 with redistilled water) were added to 2.5 cc of each filtrate, the rate of adding the reagent being constant. Within two to ten minutes after the addition of the reagent the blue colour developed was compared in a Duboseq colorimeter with that given by a standard solution of tyrosine in 0.1 N HCl. The concentrations of the standard tyrosine solutions were chosen so that they did not deviate more than ± 25 per cent from that of the test solutions. The necessary standard solutions were made by diluting a stock solution of 0.01 M tyrosine in 0.1 N HCl. The tyrosine content of the standard solution was controlled in a Beekman photometer. This photometer was, unfortunately, not available for the routine test readings. The tyrosine concentration (p. 40) calculated from the colour value of the test minus that of the blank is due to the amount of split products colourable with Folin-Ciocalteu's reagent and is thus proportional to the amount of protein hydrolyzed and therefore to the peptic activity.

Since as pointed out previously the writer did not in every detail use the standard conditions of Anson's method and since the investigation only aimed at a comparison of the enzymatic activity of premature and full-term infants, the values were expressed simply by the amount of tyrosine per ec trichloracetic acid filtrate and not in any absolute units, which are of but little interest in this connexion. For the sake of completeness an approximative calculation of the values into Northrop's pepsin units has nevertheless later been made.

The analytical procedure was controlled at frequent intervals by determining the peptic activity of a U.S.P. pepsin preparation (1:10000) stored at—15°C in a paraffined flask. Deviation from the mean value in these determinations was on the average 3.28 per cent.

Discussion of the Method.

The mucosa was only wiped clean of the layer of mucus covering its surface and not washed, in order to avoid extracting any intra-cellular pepsinogen in washing away the mucus. That this did not interfere with the accuracy of the method despite the fact that some pepsin or pepsinogen is dissolved in the mucus is evident from the good agreement in the values for the peptic activity of two proximal samples of mucosa from the same stomach (Table IX). For the same reason possible errors in measuring the surface area of the excised samples of mucosa cannot have been of any importance. The extraction of the pepsin was arbitrarily allowed to take place for 48 hours. This time was evidently sufficient, since a prolongation of it did not increase the amount of pepsin that could be extracted. That it was not unduly long was evident from the fact that the peptic activity did not decrease if the extracts were kept for one more day at 4° C.

When a proteolytic enzyme is allowed to act on an appropriate substrate under optimal conditions of pH, the rate of digestion will depend on the amount of enzyme and substrate, the temperature and the time of digestion. In the method used here, the experimental conditions are such that the rate of digestion, measured by the amount of split products formed, varies only with the amount of enzyme and is proportional to it. This is true when the amount of substrate is such that an increase will not

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speed up the rate of digestion and the temperature chosen is so low and the time of digestion so short that the formation of enzyme-inhibiting substances, or other changes in the substrate, cannot obscure the proportionality between the rate of digestion and the amount of enzyme (Baldwin 1947, Northrop 1939).

The time and temperature of digestion (10 minutes and 25°C) used by Anson and Northrop (Northrop 1939) were found to be unsuitable in these cases. Preliminary experiments showed that under these conditions the peptic activity in the youngest premature infants would have been too small for an accurate estimation by the comparative colorimetric method used. The time was therefore increased to 20 minutes and the temperature raised to 30°C.

For enzyme extracts of the strength met with in this work the amount of substrate used was sufficient, since in digestion—under the standard conditions used—with U.S.P.-pepsin of a strength equal to that of the strongest extract, the value of the split products was not changed even if the concentration of haemoglobin in the substrate was doubled.

Sources of error due to technical details.

Since ordinary distilled water made alkaline with NaOH sometimes gives a blue colour with Folin-Ciocalteu's reagent, water redistilled in a glass apparatus was used. Filter paper can either absorb split products which give a colour with Folin-Ciocalteu's reagent or contain soluble impurities giving rise to high blank values. Every new packet of filter paper was therefore examined in this respect by comparing the colour given by filtered and centrifuged samples from the same test solution. It was found that Munktell's 00 filter paper always gave a filtrate identical with the supernatant of the centrifuged sample, and it was therefore used throughout the investigation.

The blue colour formed by adding Folin-Ciocalteu's reagent to the test solution fades on standing. To counteract this source of error the test solution corresponding to the undiluted extract was in every case compared with the standard at exactly the same

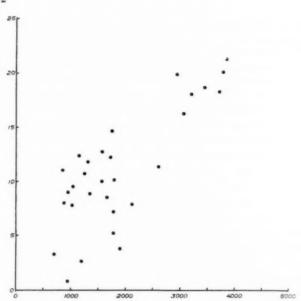


Fig. 28 a. Diagram of the Relation between the Values for the Peptic Activity of the Gastric Mucosa from the 30 Infants Examined. Cases Arranged According to Weight at Birth. Abscissa: Weight of the infants in g. Ordinate: The peptic activity expressed as milliequivalents ×10⁻⁵

Fig.

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tyrosine per cc. trichloracetic acid filtrate.

time after the addition of the reagent. The values for the undiluted extracts should therefore be fully comparable.

The unavoidable errors due to the subjective factors in comparative colorimetry have been limited as far as possible by using the same stock solution of standard tyrosine and the same equipment throughout the investigation. Furthermore, the determinations were all made by the same person.

Results.

The values obtained for the peptic activity in the gastric mucosa of premature and full-term infants are seen in diagrams a and b, Fig. 28. Each point in the diagram represents the peptic

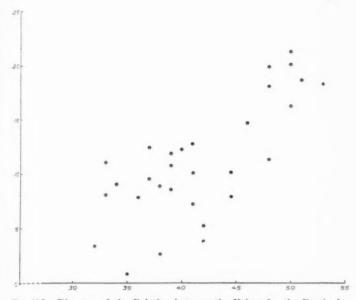


Fig. 28 b. Diagram of the Relation between the Values for the Peptic Activity of the Gastric Mucosa from the 30 Infants Examined.
 Cases Arranged According to Length at Birth.
 Abscissa: Length of the infants in cm.
 Ordinate: The peptic activity expressed as milliequivalents × 10⁻⁵ tyrosine per cc trichloracetic acid filtrate.

activity in the undiluted extract of the gastric mucosa, expressed by the amount of tyrosine in milliequivalents \times 10⁻⁵ per cc trichloracetic acid filtrate.

It is seen from the diagram (Fig. 28 a) that the marked difference between premature and full-term infants in the capacity to produce pepsin that can be assumed from the histological picture is well brought to view by the analysis of the pepsin content in the gastric mucosa. Thus not a single premature case shows a value that comes up to the lowest value of the full-term cases. It is not possible among the premature cases of 1000—2000 g to distinguish any successive increase in the pepsin content parallel to weight. There are considerable variations, but both maximum and minimum values occur fairly evenly distributed throughout the group.

Of the three cases with birth-weights between 2 000 and 3 000 g the one whose weight was just over the 2 000 g limit showed a premature value, as did the infant weighing 2 600 g born 5 weeks before term. The third infant, weighing 2 940 g, born 2 weeks before term, showed a value on the same level as these for the full-term infants.

The chemical investigation shows that the abrupt acceleration in the development of the chief cells with regard to the pepsinogen granules, that takes place in the 10th foetal month, corresponds to a similarily abrupt increase in the peptic activity during the same age. Thus it is evident from the diagram in Fig. 28 b, in which the peptic activity is correlated to the length and thereby even to the foetal age of the infants at birth, that the values for the peptic activity, which in younger infants lie at a relatively low level, increase abruptly in infants over 45 cm in length, i.e. in the tenth month.

The writer determined the peptic activity of the gastric mucosa from a starved full grown pig according to the method used in this work. A comparison showed that the peptic activity of the gastric mucosa of the full-term infants corresponded approximately to between one-fifteenth to one-tenth of that of pig mucosa.

In Table X the peptic activity in the cases examined is expressed per cm² surface area. The values are obtained as follows:

e. g. Case 49:

1) The amount of tyrosine per ce trichloracetic acid filtrate was in this case (p. 73)

 7.8×10^{-5} milliequivalents

 The amount of tyrosine in the whole digestion mixture, corresponding to the activity in 0.5 cc extract (or 11.34 mm² gastric mucosa, p. 36)

 $7.8 \times 8 \times 10^{-5}$ milliequivalents

 Amount of tyrosine liberated due to the peptic activity in 1 cm² gastric mucosa =

 $\frac{7.8 \times 8 \times 10^{-5} \times 100}{11.34} =$

 55.02×10^{-4} milliequivalents

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 $T_{\rm AHLE}$ X. Peptic Activity per cm² Gastric Mucosa from Premature and Full-term Infants.

 $T = Milliequivalents \times 10^{-4}$ tyrosine.

 $N = Northrop's pepsin units <math>\times 10^{-4}$.

	7	r	1	N
Case No.	Premature	Full-term	Premature	Full-tern
	Infa	ants	Infa	ints
	-			
48	70.5		5.1	
49	55.0		4.0	
50		149.6		10.9
51	77.6		5.6	
52	23.3		1.7	
53	62.1		4.5	
54	71.3		5.2	
55	89.6		6.5	
56	26.8		1.9	
57	56.4		4.1	
58	55.7		4.0	
59	50.8		3.7	
60	63.5		4.6	
61		131.2		9.5
62	36.7		2.7	
63	60.0		4.4	
64	87.5		6.3	
65		114.3	0.0	8.3
66		141.1		10.2
67		139.7		10.1
68	83.2	100.1	6.0	10,1
69	103.0			
	75.5		7.5	
			5.5	
	86.1		6.2	
72	67.7	107.0	4.9	
73	-0-	127.0		9.2
74	79.7		5.8	
75	18.3		1.3	
76	5.6		0.4	
77		128.4		9.3

In Table X the values of the peptic activity are also given approximately calculated in Northrop's units (Northrop 1939). Northrop defines the

proteinase unit used in his laboratory as the amount of enzyme that — under the condition of the method — digests haemoglobin at an initial rate such that there is liberated per minute an amount of split products not precipitated by the trichloracetic acid, which gives the same colour with the phenol reagent as one milliequivalent of tyrosine.

The calculation of the results into these units is best seen from an example:

Case 49: 1) Tyrosine liberated during digestion — under the standard conditions used in this work — by the pepsin in 1 cm² gastric mucosa =

 55.0×10^{-4} milliequivalents.

2) Tyrosine liberated during 1 minute digestion =

$$\frac{55.0\times10^{-4}}{20} \text{ milliequivalents.}$$

 Tyrosine liberated during 1 minute digestion at the standard temperature (35.5° C) 1 of Northrop =

$$\frac{55.0\times10^{-4}}{20}+\frac{55.0\times10^{-4}\times0.082\times5.5}{20}$$

 4.0×10^{-4} milliequivalents.

4) As 1 Northrop unit liberates 1 milliequivalent then the activity in 1 cm² gastric mucosa in this case must be 4.0 × 10⁻⁴ proteinase units.

Summary and Discussion of the Histological and Chemical Results.

The writer's investigation on pepsin shows that at birth a difference exists between premature and full-term infants in the pepsin-producing capacity of their gastric mucous membranes. Histologically, the maturity of those cells which later produce pepsin, i. e. the chief cells, progresses so slowly during the 8th and 9th foetal months that no increase in amount of their specific

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 $^{^1}$ Northrop and collaborators now use $25^{\circ}\,\mathrm{C}$ as the temperature of digestion, but retain $35.5^{\circ}\,\mathrm{C}$, the digestion temperature previously used in his laboratory, as the standard temperature in the definition of the unit. $0.082 = \mathrm{the}$ factor of increase in rate of digestion with $+~1^{\circ}\,\mathrm{C}.$

granules could be observed, although the mucous membrane in general underwent considerable changes. In the material examined, the granules were scanty in the youngest as well as in the older premature infants. Since, however, the full-term infants practically without exception showed basally in the mucosa of the fundic region a marked border of granule-bearing cells, the development of granules must accelerate abruptly some time during the 10th foetal month. The difference in this respect between premature and full-term infants was so marked that a mathematical calculation appeared superfluous. It is thus possible to conclude that, up to the 10th foetal month, there is an almost complete lack of pepsinogen granules.

Chemical determination of the pepsin content also revealed a definite difference between the premature and full-term groups.

Since earlier investigations, as pointed out elsewhere (p. 8) have convincingly demonstrated that the pepsin content of the gastric mucosa varies with the content of the pepsinogen granules. it is surprising that the differences in peptic activity between premature and full-term infants found in the chemically examined eases of this material, although evident, were not always as marked as would seem likely from the histological examination. This probably depended on the fact that in such low concentrations of enzymes as were present in the material examined, the values were influenced by the amount of pepsin which during a continuous although scanty secretion had been absorbed into the mucous border of the surface epithelium. As is seen from Fig. 27, the mucous cells of the surface epithelium are well developed even in the youngest premature infants. Thus, both in the premature and the full-term cases, pepsin-saturated mucus can affect the actual values. It is probable that the marked chemical difference which must exist between premature and full-term infants, if the histological picture is considered, was thus somewhat evened out in the chemical material.

With somewhat higher values for the peptic activity the direct proportionality between the amount of granules and the peptic activity is more evident. The writer investigated a full-term infant, aged $4^{1/2}$ months. The mucous membrane (Fig. 3) showed a belt of granules 3—4

times broader than in a newborn full-term infant. This is seen on a comparison with the case in Fig. 23. The peptic activity of the $4^{3}/_{2}$ month old infant was also about four times greater than that of this case.

The results indicate that the gastric juice secreted by the premature gastric mucosa must be very deficient in its protein-splitting capacity.

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Part II.

PANCREAS PROTEINASES.

Review of the Literature.

The proteolytic enzymes in the pancreas have usually been studied by chemical methods, probably since the various enzymes produced cannot be traced back to special types of pancreatic cells. Several enzymes, proteolytic and other, can be thought to be associated with the granules which are so typical of the acinar cells. The present writer also used chemical methods of investigation, but in addition studied the respective specimens histologically in order to ascertain the general degree of maturity of the pancreas cells at various foetal stages. As in the case of the chief cells of the gastric mucosa, the amount of granules was taken as a measure of the functional capacity of the cell. This can be considered as justified, since it is now generally accepted that the activity of the enzymes in the pancreatic extract is correlated to the quantity of secretory granules in the cells (BABKIN 1944).

CLAUDE BERNARD in 1856 was the first to point out the presence of granules in the acinar cells of the pancreas. Heidenhain observed how the amount of granules changed according to the phases of secretion, since starving animals showed more plentiful granules than digesting ones. This was confirmed by Grützner (1878). Langstroth, Mac Rae and Komarov (1939) showed in the dog that an equilibrium is established between secretion and the formation of new granules. On physiological stimulation the amount of granules in the cells decreases only to a certain degree before the new formation starts.

KÜHNE (1867) observed the protein-splitting capacity of the pancreatic juice and named the active principle trypsin.

^{4 - 48619} Birgitta Werner

The Foetal Development of the Proteolytic System in the Pancreas.

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Those workers who have studied the foetal development of the stomach have usually also shown an interest in the development of the pancreas. Briefly, it can be stated that these investigations show that trypsin and lipase are present at birth and probably even from the 4th foetal month on (Keene & Hewer 1929). According to the majority of writers (Zweifel 1874, Keene & Hewer 1929, Klumpp & Neale 1930) amylase does not, however, occur regularly at birth.

In discussing the question of the trypsin content special attention must be paid to its occurrence in inactivated or activated form. Until the discovery of enterokinase in 1899 by the Paviov school, the results of investigations on the presence of trypsin showed a great lack of agreement, probably since in some cases trypsin predominated in the extract and in others trypsinogen. Thus Hammarsten (1874) did not consider himself justified in drawing any conclusions from the investigations he had made on the human pancreas, since he was evidently aware that some detail, as yet unexplained, could conceal the true conditions.

ZWEIFEL (1874) stated, on the basis of three cases examined, that trypsin is present in newborn infants. Langendorff (1879) investigated six human foetuses from the earlier foetal months and was able to demonstrate trypsin in three cases (5th and 6th months) but not in the other three (4th, 5th and 6th months). Jakubowitch (1898) found tryptic activity in the pancreas of infants 5 days old. Jaeggy (1907) found no trypsin in two cases from the 6th and 9th foetal months.

In 1909, IBRAHIM made a thorough qualitative investigation of the occurrence of enterokinase and trypsin in nine cases. These nine cases consisted of 2 full-term infants, 3 premature infants weighing 2 500 g, 820 g and 720 g and 3 foetuses weighing approximately 400 g and 1 weighing 150 g. He was able to demonstrate enterokinase activity in the intestinal mucous membrane of foetuses down to a weight of 390 g.

He scraped the mucosa with a blunt scalpel and diluted the material with 20 times its volume of distilled water to which toluene had been added. This solution had no protein-splitting capacity. The enterokinase was then demonstrated in the solution by its ability to activate pancreatic extracts.

IBRAHIM's investigations showed that trypsinogen can be activated by the intestinal juice of both premature and full-term infants. According to a generally accepted opinion, only a very minute quantity of activator is necessary for activation of trypsinogen, since as soon as some trypsin is formed, this activates the remainder of the trypsinogen. Thus, once its presence in premature infants has been proved, it is very difficult to imagine that these infants may suffer from a deficiency of enterokinase. In this work the enterokinase activity of newborns has therefore not been investigated.

IBRAHIM investigated the protein-splitting capacity of pancreatic extracts from his nine cases, using enterokinase from full-term infants as an activator. He found that trypsin was present in cases weighing as little as 390 g. Its presence was doubtful in the case weighing 150 g. Keene & Hewer (1929) made a qualitative determination of trypsin in seventeen human foetuses, of which the youngest was from the 4th foetal month. They found trypsin to be consistently present from this stage on. They also made histological studies of the pancreas and stated that they found incipient granule formation in the cells as early as the 3rd foetal month.

It can be seen from this review of the literature that the earlier investigators were interested chiefly in determining how early in foetal life the different enzymes could be demonstrated and in ascertaining the normal enzymatic condition in full-term infants. Moreover, the investigations were all qualitative. No comparative quantitative studies of the pancreas proteinase activity in premature and full-term infants by chemical and histological technique have hitherto been made. The present work was meant to meet this deficiency.

The Writer's Investigations.

Material.

The pancreases of 41 of the cases examined as to their persinogen granules were studied histologically (Table XIII) with the stress laid on the granules of the exocrine cells. In 24 cases (Table XI) the protein-splitting capacity of the pancreatic extract was determined. In studying the pancreas the presence of several enzymes makes the histological picture somewhat difficult to interpret and the main stress has therefore been laid on the chemical investigation.

The material is not large but is nevertheless larger than that of earlier investigators. Keene & Hewer had, it is true, 17 cases in their material, but a number of them were from the early prenatal months, and are therefore of little interest in this connexion. Moreover, their investigations were only qualitative.

As regards the sources of error in the present material, they are on the whole the same as those discussed earlier in connexion with the work on pepsin (p. 21). The specimens from the pancreas were prepared as early after death as the gastric specimens. Since it was not possible to obtain an ideal material, only such premature infants were selected in which the cause of death could be assumed not to have influenced the enzyme system of the pancreas (Table XI). The administration of food does not appear to play any decisive rôle as regards the granule formation and content of proteinase in the pancreas since, as mentioned earlier (p. 49) an equilibrium is in all probability established between secretion and new formation of enzymes in the cells.

As is evident from table XI the material studied chemically derives from varying weight and age groups. Most of the premature infants lived about 24 hours.

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Table XI. Pancreas Material Studied Chemically.

The Cases Arranged in Groups According to Weight, Length, Time of Survival and Cause of Death.

Weight at Birth, g	No. of Cases	Length at Birth, cm	No. of Cases
< 1000	3	> 30 < 35	1
1 000 < 1 500	4	$\equiv 35 < 40 \dots$	7
1 500 < 2 000	7	₹ 40 < 45 · · · · · · · · · · · · · · · · · ·	7
$\geq 2000 < 2500\dots$	2	$\geq 45 < 50 \dots$	5
S 2 500 < 3 000	2	₹ 50	4
₹ 3 000	6		24
	24	,	

		No. of	Cases
	Time of Survival		Full-term
0	minutes	. 2	2
0—some ≤ 24	hours		3
= 24 > 24 < 48			1
2-3	davs		1
5	*		0
3	weeks		1
		16	8
		Tota	1 24
		No. of	Cases
	Cause of Death	Premature 1	Full-term
Congenital	debility (only)	. 8	_
-	during parturition		0
Pulmonary atelectasis			0
Intracranial	haemorrhage	. 2	4
Pulmonary	atelectasis + Intracranial haemor-		
rhage		. 0	1
Aspiration of amniotic fluid		. 0	1
Congenital heart disease		. 0	1
Intrauterine asphyxia		. 0	1
Suprarenal	apoplexy	. 1	0
		16	8
		W.11	

 $^{^{1}}$ Birth-weight $\,\leq 2\,500$ g.

Chemical Determination of the Proteinase Content of the Pancreas.

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1. The pancreas was excised and freed from vessels and coarse connective and adipose tissue. After a piece had been removed for histological examination, the remainder was sectioned into thin slices and ground to a fine powder after freezing in liquid air.

2. Water and fat were extracted from the powder with collacetone. The acetone was drawn off by suction and the powder repeatedly washed on the filter with acetone.

3. The defatted dry powder was extracted with 1 ml of glycer (containing 13 per cent of water) per 40 mg of dry powder Extraction took place for 4 hours at 30° C, in small covered extraction vessels of thin glass (diameter of base 2 cm, height 4 cm. During extraction the samples were stirred every 15 minutes with thin glass rods which remained in the mixtures for the time of extraction. Irrespective of the stirring, the powdered material was distributed fairly evenly in the fluid owing to the viscosity of the glycerol.

4. After extraction the sample was diluted with an equal volume of distilled water. Tissue particles were separated from the fluid by means of simultaneous centrifugation and filtration. Centrifugation alone did not yield a clear supernatant and filtration proved impractical owing to the viscosity of the fluid and its small quantity (sometimes only 2 ce). It was therefore necessary to use combined filtration and centrifugation. This was performed by placing a piece of glass tubing, 47×10 mm, inside a centrifuge tube, 110×13 mm, with its out-turned upper edge resting on the mouth of the centrifuge tube and its lower end closed with a silk membrane. The extract was poured into the tubing. On centrifugation an absolutely clear solution was obtained.

5. To each ce of this solution 5 mg of enterokinase powder was added and activation of the trypsinogen in the mixture allowed to take place for 12 hours at 4° C.

The enterokinase was prepared in principle according to

Kunitz' method (Kunitz 1938) based on fractional precipitation with ammonium sulphate of the duodenal mucus from pigs starved for 24 hours.

To prepare enterokinase dry powder Kunitz precipitated the dialyzed solution of purified enterokinase with cold alcohol. By freezing-drying of the dialysate the writer obtained an enterokinase powder fully soluble in water. This was not the case with Kunitz' alcohol precipitate which, according to the experience of the writer, becomes partly insoluble in water after drying. The enterokinase powder obtained by this method had no protein-splitting capacity. It could be kept for months at —15° C without deterioration.

6. The proteolytic activity in the activated glycerol extract was determined according to Anson (Northrop 1939). As in the case of pepsin, determinations of the activity were made not only on the extract but even on some dilutions of it. Distilled water was used as the diluent. The extract contained 20 mg pancreas dry-powder per ce; dilutions were made corresponding to 15 mg and 5 mg pancreas dry-powder per ce. The procedure for the determination was essentially the same as that used for the peptic activity (p. 38). The pH of digestion was, of course, different (7.5), and the substrate therefore (prepared according to Anson) of a somewhat different composition: 8 ce of 1 N NaOH, 72 cc water, 36 g urea and 10 cc of a 22 per cent haemoglobin solution were mixed and placed in a water bath at 25° C for 30—60 minutes for denaturation of the haemoglobin. 10 cc 1 M KH₂PO₄ and 4 g of urea were then added.

The digestion time was here 10 instead of 20 minutes, since the former time was sufficient, even in the weakest extracts, to give colour values high enough to be determined with accuracy, and it is important to limit the time of digestion as much as possible in working with pancreatic extracts, owing to the presence of inhibitory substances. For technical reasons the digestion temperature was the same as for the pepsin determinations, i. e. 30° C.

After inactivation of the enzyme with trichloracetic acid the

sample was allowed to stand for 30 minutes before filtration. The further procedure was the same as that used for pepsin.

Determinations of proteinase activity on defatted panereas powder from pigs were run regularly as a control of the technique. Panereas powder from the same stock, kept at —15° C, was used throughout for these controls. Deviation from the mean value in these determinations was on an average 4.0 per cent.

Discussion of the Method.

Owing to their very small size, it was not possible to grind the specimens without previous freezing. Control experiments on pig pancreas showed that the proteinase was not destroyed by treatment with liquid air.

Extraction for four hours proved to be satisfactory under the conditions of the experiments. Doubling the extraction time did not increase the figures for the activity. The same values for the enzyme content of pig pancreas were obtained with or without stirring during extraction.

5 mg enterokinase per cc of glycerol extract proved to be sufficient for complete activation of the enzyme extract, since an addition of 10 or 15 mg did not give higher values.

The necessity of using controlled filter paper has been pointed out earlier (p. 41).

There was sufficient excess of the substrate in these determinations, since in estimating enzymatic activity of the most active glycerol extracts practically the same values were obtained whether the ordinary or an increased haemoglobin concentration in the substrate was used. In pancreatic extracts an exact proportionality between the strength of the enzyme and the amount of split products cannot be expected, due to the trypsin-inhibitory substances (Northrop 1939, Baldwin 1947). Nevertheless, when as in this work the enzyme concentration is low and the digestion time short, the amount of the split products is practically proportional to the strength of the enzyme.

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Results.

The relation between full-term and premature infants as regards the activity in the pancreas proteinase system is seen from diagrams a and b, Fig. 29. The points give the activity of the undiluted extract from the defatted pancreas dry-powder. As a comparison, the activity in the pancreas of a full-grown pig is shown, the extract being prepared in the same manner as for the ordinary specimens.

In Table XII the values for the proteinase activity of the cases per $10~\rm mg$ pancreas powder are given in milliequivalents $\times\,10^{-4}$ tyrosine and in Northrop's proteinase units. The calculation into Northrop's units is similar to that for the peptic activity (p. 46).

Although the number of cases investigated is too small to give a final picture of the proteolytic activity in the pancreas of newborns, the material nevertheless emphasizes a marked difference in the values for premature infants weighing 1 000—2 000 g at birth and full-term infants. Whereas the values, with one exception, are extremely low in the former group, the proteinase activity in the latter can be high, in some cases corresponding to 85 per cent of the strength of the enzyme in pancreatic extracts from full-grown pigs.

Whereas the full-term infant has a panereas well equipped to split proteins, the premature infants in the forementioned weight group would be handicapped in this respect. A single deviating case (Case 69) with a higher value indicates that a larger material might have shown a somewhat better situation for the prematures. It cannot with certainty be concluded from the investigations whether the enzymatic activity increases gradually until it reaches full-term values or whether this increase takes place abruptly, as is the case for pepsin.

 $^{^1}$ The factor of increase in the rate of digestion with $1\,^\circ$ C is 0.074 for trypsin.

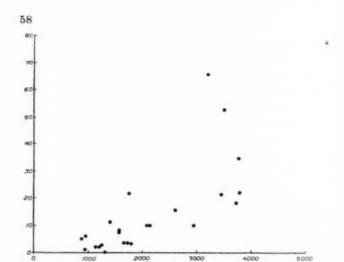


Fig. 29 a. Diagram of the Relation between the Values for the Proteolytic Activity of Pancreas Dry Powder from the 24 Infants Examined. Cases Arranged According to Weight at Birth. Abscissa: Weight of the infants in g. Ordinate: The proteolytic activity expressed as milliequivalents

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 $\times 10^{-5}$ tyrosine per cc trichloracetic acid filtrate.

O = Proteolytic activity of dry powder from pig pancreas.

Histological Treatment of the Material.

In 41 cases the pancreas was examined histologically.

The pancreatic specimens were mainly taken from the same infants as the gastric material. Weight and length are seen from Table XIII and the time of survival and cause of death from Table XIV.

The pancreas was fixed according to Regaud and stained according to Bowie in the same way as the specimens from the stomach. As was the case in the gastric specimens, the zymogen granules stained violet in contrast to the other tissue, which stained yellow.

Results.

No zymogen granules could be observed in the youngest cases weighing 600, 750 and 950 g (Fig. 34).

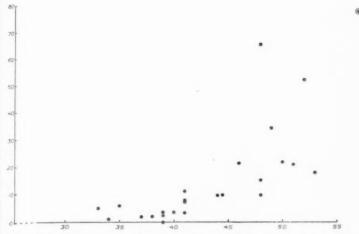


Fig. 29 b. Diagram of the Relation between the Values for the Proteolytic Activity of Pancreas Dry Powder from the 24 Infants Examined. Cases Arranged According to Length at Birth. Abscissa: Length of the infants in cm. Ordinate: The proteolytic activity expressed as milliequivalents $\times~10^{-5}$ tyrosine per cc trichloracetic acid filtrate.

Proteolytic activity of dry powder from pig pancreas.

In the weight-group of 1 000 to 2 000 g the granules were lacking or only beginning to appear (Plate IV, Figs 30, 35, 36, 38, 40, 42, 44). With one exception, Case 69 (Fig. 45), which showed fairly plentiful granules (and high tryptic activity!), these cases had scanty granules as compared to the full-term ones.

The cases between 2 000 and 2 500 g varied as to the amount of cells containing granules but in most of them an incipient formation of granules could be observed (Fig. 31).

In cases over 3 000 g the granules were usually extremely plentiful, being in some cases almost as numerous as in the panereas from older infants (Plate III, Figs 32, 37, 39, 41, 43, 46 and 33).

The three cases weighing more than 2 500 but less than 3 000 g all showed pictures transitional between premature and full-term ones (Fig. 47).

Table XII. Proteolytic Activity of 100mg Pancreas Dry Powder from Premature and Full-term Infants.

 $T = Milliequivalents \times 10^{-4}$ tyrosine.

 $N = Northrop's proteinase units \times 10^{-4}$.

	1	Г	2	N.
Case No.	Premature	Full-term	Premature	Full-to
	Infants		Infants	
46	80.0		11.2	
55	64.0		9.0	
57	40.0		5.6	
58	80.0		11.2	
59	27.2		3.8	
60	8.0		1.1	
61		169.6		23.0
63	28.8		4.1	
34	16.0		2.3	
86		176.8		24.9
37		80.0		11.2
38	0		0	
39	173.6		24.4	
70	20.0		2.8	
71	28.8		4.1	
3		522.4		73.5
14		124.0		17.4
75	16.8		2,4	
76	48.0		6.8	
17		144.8		20.4
78		275.2		38.7
79	90.4		12.7	
30		419.2		59.0
31	60.8		8.6	

In two infants with a weight under 2500 g but despite this full-term, since each of them had a full-term twin, the executive pancreatic cells were rich in zymogen granules (Figs 48, 49).

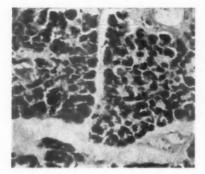


Plate III. Pancreas from a full-term infant with a weight at birth of 3450 g. Death during parturition due to intervention (perforatio capitis). The exocrine tissue rich in coarse violet zymogen granules.

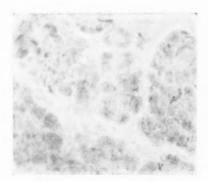
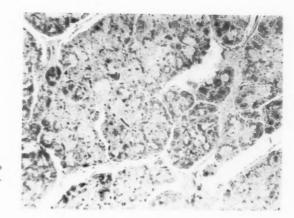


Plate IV. Pancreas from a premature infant with a weight at birth of 1250 g. Death 7 hours after birth due to congenital debility. The granule formation just beginning.

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F) 30. Case No 54.

B 4-weight 1790 g.
P) nature pancreas. No
zy ogen granules discern-

En regement 125 ×

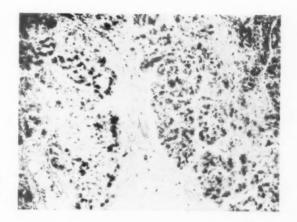


Fig. 31. Case No 58, Birth-weight 2 120 g. Premature pancreas with incipient granule formation. Enlargement 125 ×

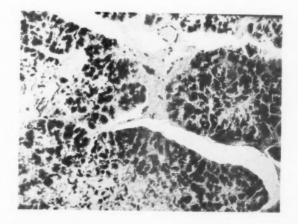


Fig. 32. Case No 17. Birth-weight 4 080 g. Full-term pancreas rich in zymogen granules. Enlargement 125 ×

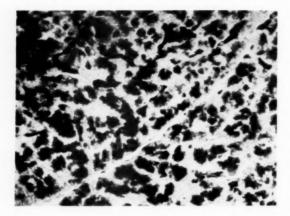


Fig. 33. Pancreas from a full-term infant one yes of age.

The exocrine tissue is h in zymogen granules.

Enlargement 188 ×

B

ul

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Fig. 34. Case No 25. Birth-weight 600 g. Premature pancreas without zymogen granules. Enlargement 325 ×

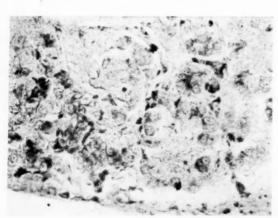
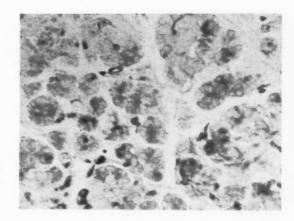


Fig. 35. Case No 1. Birth-weight 1 100 g. Premature pancreas. Granule formation just beginning. Enlargement 325 ×



 $\begin{array}{lll} F_1 & 36. \ Case \ No \ 70, \\ B_1 & \text{s-weight} \ 1 \ 250 \ g, \\ P_1 & \text{nature pancreas}, \ Granul & \text{formation just beginni} \\ \vdots & \vdots & \vdots \\ E_{11} & \text{rgement} \ 325 \times \end{array}$

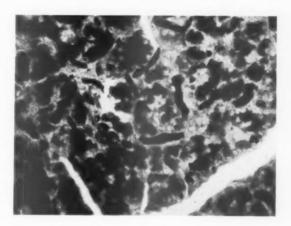


Fig. 37. Case No 37. Birth-weight > 3 000 g. Full-term pancreas rich in coarse zymogen granules. Enlargement 325 \times

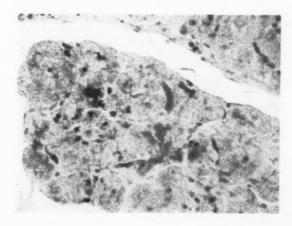


Fig. 38. Case No 7. Birth-weight 1170 g. Premature pancreas without zymogen granules. Enlargement $325 \times$

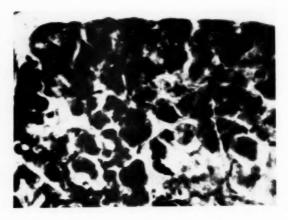


Fig. 39, Case No 16, Birth-weight 3 340 g, Full-term pancreas ric in coarse zymogen granuli Enlargement 325 s

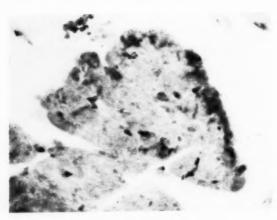


Fig. 40. Case No 27. Birth-weight 1 350 g. Premature pancreas. Granule formation just beginning. Enlargement 325 ×

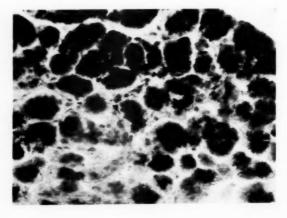
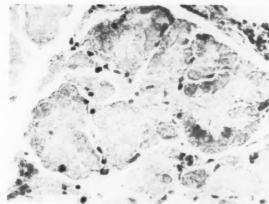
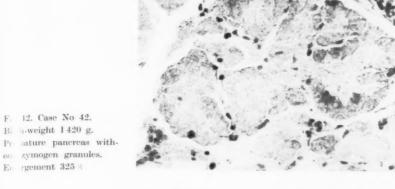


Fig. 41. Case No 4. Birth-weight 3 620 g. Full-term panereas rich in coarse zymogen granules. Enlargement 325 ×





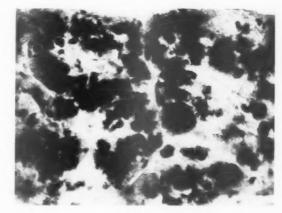


Fig. 43. Case No 10. Birth-weight 3 610 g. Full-term pancreas rather rich in zymogen granules. Enlargement 325 \times

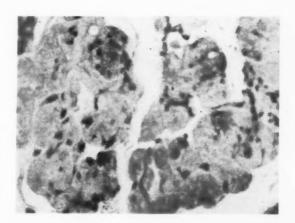


Fig. 44. Case No 40. Birth-weight 1780 g. Premature pancreas without zymogen granules. Enlargement $325 \times$

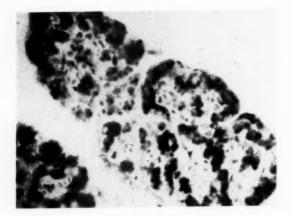


Fig. 45. Case No 69.
Birth-weight 1 750 g.
Premature pancreas ra rrich in zymogen gram s.
Enlargement 325 ×

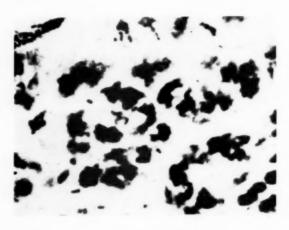


Fig. 46. Case No 3.
Birth-weight 3 680 g.
Full-term pancreas rich in coarse zymogen granules.
Enlargement 325 ×

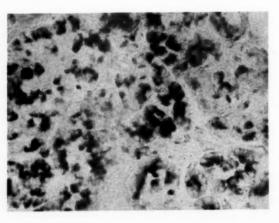
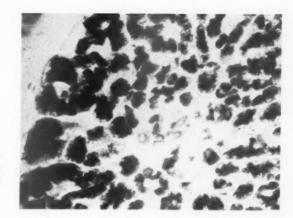


Fig. 47, Case No 12.

Birth-weight 2 540 g (born 5 weeks before calculated time).

Pancreas rather rich in zymogen granules.

Enlargement 325 ×



F 48. Case No 6.
B h-weight 2440 g (fullte a despite the low weight yin). Pancreas rich in se zymogen granules.
E argement 325 ×

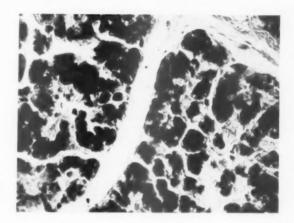


Fig. 49. Case No 36.
Birth-weight 2 270 g (full-term despite the low weight
—twin). Pancreas rich in coarse zymogen granules.

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TABLE XIII. Pancreas Material Studied Histologically.

The Cases Arranged in Groups According to Weight and Length.

Weight at Birth, g	No. of Cases	Length at Birth, em	No. of Cases
< 1 000	3	₹ 30 < 35	2
1 000 < 1 500	12	$\equiv 35 < 40 \dots$	11
1 500 < 2 000	6	₹ 40 < 45	8
2 000 < 2 500	5	\geq 45 < 50	5
2 500 < 3 000	3	₹ 50	15
3 000	12		41
	41		

The histological investigations thus brought to view a marked difference between premature and full-term pancreatic tissue with respect to the amount of granules in the exocrine cells. It seems, however, likely that the development here takes place more gradually than is the case with the pepsin-producing elements of the gastric mucosa (Figs 30, 31, 32).

Discussion of the results.

The possibility cannot be excluded that in adults the granules of the pancreas are related not only to proteinase, but also to amylase and lipase.

Amylase can be disregarded in the present investigations since, according to most workers, its presence cannot be demonstrated in full-term newborn infants. Thus Zweifel found no amylase in his cases. Klumpp & Neale (1930) in a material comprising infants of which the youngest was one month, found an insignificant quantity of amylase in the pancreatic juice. Keene & Hewer did not find it regularly in the pancreas of full-term infants. Farber, Maddock and Shwachmann—reported by Smith 1946—found no amylase in the pancreas of full-term newborn infants.

The presence of lipase can, it is true, be demonstrated at birth and even as early as in the 4th foetal month (Ibrahim 1909, Keene & Hewer 1929). Farber, Maddock and Shwachmann

^{5 - 48619} Birgitta Werner

Table XIV. Pancreas Material Studied Histologically.

Time of Survival and Causes of Death of the Infants.

	No. of	No. of Cases		
Time of Survival	Premature 1	Full-tern		
0—some minutes	4	7		
< 24 hours	11	0		
₹ 24 < 48 hours	7	3		
2-3 days	3	*3		
5 *	1	0		
9 *	0	1		
3 weeks	0	1		
	26	15		
	Total 41			

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	No. of Cases		
Cause of Death	Premature 1	Full-term	
Congenital debility (only)	10	_	
Intervention during parturition	2	3	
Pulmonary atelectasis	6	•)	
Intracranial haemorrhage	2	1	
Pulmonary atelectasis + Intracranial			
haemorrhage	3	3	
Bronchopneumonia	1	1	
Congenital heart disease	0	3	
Intrauterine asphyxia	1	•)	
Suprarenal apoplexy	1	0	
	26	15	
	Tota	1 41	

(1946) however, who investigated the presence of trypsin, lipase and amylase in children from newborn infants up to ten-year-olds, pointed out that there is very insignificant lipase activity during the first months of life. It might in this work have been of interest to study the activity of lipase in addition to that of proteinase in order to ascertain to what degree the granules could eventually be referred to lipase. This was, however,

¹ Birth-Weight < 2 500 g.

not done, since the glands to be analyzed were of such a small size that the writer preferred to dispose of all the available material for the histological and chemical studies on proteinase. GLICK (1936) and LINDERSTRØM-LANG & HOLTER (1940) showed the presence of lipase in the pyloric region of the stomach. With the histological technique used in the present work it was not possible to demonstrate any granules in this region and it seems therefore probable that pancreatic lipase likewise has no relation to the granules stainable by Bowie's method.

In the writer's material the degree of maturity of the experine cells in various foetal stages is in good agreement with the chemical findings. A marked difference between premature and full-term infants can be demonstrated in the proteolytic activity and in the amount of granules of the experime pancreatic cells.

Summary.

The gastric mucous membrane of 70 newborn infants (47 premature) was examined histologically for the occurrence and amount of pepsinogen granules. The peptic activity of the gastric mucosa was determined in 30 cases (22 premature). In 41 cases (26 premature) the pancreas was studied histologically in order to determine the developmental stage of the exocrine cells, the amount of zymogen granules being taken to indicate their maturity. In 24 cases (16 premature) the proteolytic activity of the pancreas was determined chemically.

The following conclusions can be drawn from the investigations:

Premature infants under 2 500 g show no or only extremely few pepsinogen granules in their chief cells. In the full-term infants over 3 000 g, on the other hand, the granules, despite considerable variations in amount, are always present and in far greater number than in any of the premature cases, although they are confined to the basal parts of the main gastric glands, whereas in the adult, as well known, they occupy about three-fourths of the gland. The cases between 2 500 and 3 000 g show variations between the premature and full-term pictures. It is

therefore evident that the production of pepsinogen granules is abruptly accelerated very late in foetal life.

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A distinct difference in peptic activity can be demonstrated between premature and full-term newborn infants although it is not as marked as could be expected from the striking difference in the amounts of pepsinogen granules in the chief cells of the two groups of infants. The gastric mucosa of the full-term infant is per unit surface area considerably richer in pepsin than that of the premature infant. In comparison to the gastric mucosa of an adult, however, that of the full-term calls is poor in pepsin. Thus the pepsin content of the gastric mucosa of a full-term infant per unit surface area corresponds to only about 10 per cent of that of a human adult or of a full-grown 1.2.

On chemical and histological investigation the pancreas shows an extremely immature picture in premature infants with a bindreweight under 2 000 g. The difference between premature and full-term infants is still more marked here than in the gastric mucosa. Whereas the proteolytic activity of the pancreas of full-term infants is considerable—corresponding in some cases to up to 85 per cent of that of a full-grown pig—the pancreas of the premature infants shows little or no activity.

The histological picture of the pancreas is in good agreement with the chemical findings. In the youngest prematures there is a complete absence of zymogen granules and thus in all probability a lack of proteinase production in the exocrine cells. In cases between 1 000 and 2 000 g the granules are absent or only beginning to appear, and up to 2 500 g they are scanty. In the full-term infant over 3 000 g the granules are plentiful, in some cases giving a picture resembling that of the adult pancreas. The cases between 2 500 and 3 000 g show a picture transitional between those of the younger premature and the full-term cases.

If it can be assumed that in the full-term infant pepsin plays a rôle in the digestion of protein, then the premature infant with its insignificant amount of pepsinogen granules and low peptic capacity must be handicapped in this respect. Even if the importance of pepsin in the digestion of protein in full-term infants can be disputed, the rôle of the pancreas is

indisputable. The premature infant weighing less than 2 000 g at birth shows such low values for pancreas proteinases and such an immature histological picture of the exocrine pancreatic cells that, compared to the full-term infant, it must be considered as very poorly equipped for the task of protein digestion — a fact that should be kept in mind in chosing an adequate food for the premature infant.

Case Records.

	Details of interest	I	I	The mother of the infant re- ceived Morphine 0.02 g + Pheno- barbital 0.10 g 24 hours before parturition	1		The infant, who
betw	erval in hours reen last meal and death	+	4	1	No food given	7	No
	Cause of death	27 hours Congenital Debil- ity	48 hours Pulmonary Ate- lectasis	Intracranial Hae- morrhage	Intrauterine Asphyxia	10 hours Congenital Debil- 12. Trituscential Haemorrhage + +Pulmonary Archestasis	" a hour Pulmonary Ate-
	Time of survival	27 hours	48 hours	e	5 min.	10 hours	"z hour
Pancreas	Pro- teolytic activity		1	1	1		1
	Granules of the exocrine cells in the histological section	Incipient but scanty granule formation (Fig. 35)	Abundant coarse granules	Abundant coarse granules (Fig. 46)	Abundant coarse granules (Fig. 41)		Abundant coarse
18	Peptic activ- ity	and the second	1	1	1		
Gastric Mucosa	Pepsinogen granules in the histological section of the mucosa	Sparse pepsinogen granules in single chief cells	A border of pep- sinogen granules discernible	A marked border of pepsinogen granules	A marked border of pepsinogen granules (Fig. 12)	Pepsinogen gran- ules in rather many chief cells (Fig. 17)	A marked border
Length in em.		36	90	55	12	45	00
	Weight Length in g. in cm.	1100	3060	3680	3620	2070	2440
	Саве No.	1. 2861/44 Allm.B.B.	2. 532/44 Sachs' Hosp.	3. 3792/44 Söder- sjukh.	4. 3835/44 Söder- sjukh.	5. 3928/44 Söder- sjuch.	6.

							07
The infant, who	was been at term had a twin with a weight of 3100 g and a length of 50 cm.	1			I		weeks before 5 weeks before calculated time had a twin with a weight of 2211 g and a length of 50 cm.
	given	22	00	20	ಣ	4	13
1,2 hour Puhnonary Ate-	And Reliables	24 hours Congenital Debil- ity	24 hours Congenital Debil- ity.+Pulmonary Atelectasis	22 hours Congenital Debil- ity+Pulmonary Atelectasis	48 hours Congenital Heart Disease	5 hours Congenital Debil- ity+Pulmonary Atelectasis	38 hours Intracranial Hac- morthage + Pul- monary Atelec- tasis
1,2 hour		24 hours	24 hours	22 hours	48 hours	5 hours	38 hours
		1	1	1	1	1	
Abundant coarse	48) (F.1g.	No granules dis- cernible (Fig. 38)	Scarve incipient granule forma- tion in some areas	Incipient granule formation	Abundant coarse granules (Fig. 43)	Incipient granule formation	Rather abundant granules (Fig. 47)
						J	1
A marked border	granules (Fig. 15)	No pepsinogen granules dis- cernible	Pepsinogen gran- ules in single chief cells	Pepsinogen gran- ules in single chief cells (Plate II)	Scattered groups of pepsinogen granules	No pepsinogen granules dis- cernible	Sparse pepsino- gen granules in single chief cells
0.0		37	37	9	15	9	19
2440		1170	1130	1560	3610	1490	2540
1793/44	Söder- sjukh.	7. 324/45 Sachs' Hosp.	8. 377/45 Sachs' Hosp.	9. 380/45 Sachs' Hosp.	10. 394/45 Sachs' Hosp.	11. 416/45 Sachs' Hosp.	12. 464/45 Sachs; Hosp.

	Details of interest	1	1	1	1		Post mortem exa-
	erval in hours ween last meal and death	No food given	+	1	1 .		-
	Cause of death	5 hours Congenital Debil- ity	Congenital Debil- ity+Intra- cranial Haemor- rhage	Abortion Operation	40 hours Bronchopneumo- nia (aspiration of amniotic fluid)	morrhage Put- monary Atchec- tasis	Intrauterine As-
	Time of survival	5 hours	3 days	1	40 hours	the factor	0
	Pro- teolytic activity	1	1	1			
Pancreas	Granules of the exocrine cells in the histological section		1	1	Abundant coarse granules (Fig. 39)	Abundant cours granules (Fig. 32)	Abundant gran- ules
18	Peptic activ- ity	1	1				
Gastrie Mucosa	Pepsinogen granules in the histological section of the mucosa	No pepsinogen granules dis- cernible	Here and there small groups of pepsinogen granules (Fig. 25)	Sparse pepsino- gen granules in single chief cells	A marked border of pepsinogen granules (Plate 1)	A marked border of pepsinogen granules (Fig. 8)	A marked border of pepsinogen granules
	Length in cm.	39	7	#	20	10	53
	Weight Length in g. in cm.	1450	1695	006	3340	080†	4020
	Саме No.	13. 1568/45 Allm. B.B.	14. 475/45 Sachs' Hosp.	15. Ab. op. 29/6 -45 Allm. B.B.	16. 595/45 Sachs' Hosp.	17, 587/45 Sachs' Hosp.	18. 1205/45 Karol.

							0.0
	Post mortem exa- riantion in this case as late as 3 hours after death but spe- emen kept in refrigerator	1		1	1	Ĭ	1
		85 50	1	4.5	6. FC	4	No food given
tasis	Intrauterine As-	25 hours Congenital Debil- ity+Pulmonary Atelectasis	Congenital Heart Disease+Mon- golism	4 hours Congenital Debil- ity+Intra- cranial Haemor- rhage	31 hours Congenital Debil- ity+Intra- cranial Haemor- rhage	Congenital Debil.	Intracranial Hae- morrhage+Pul- monary Atelec- tasis
	0	25 hours	9 days	4 hours	31 hours	5 days	1/2 hour
				1	L		1
	Abundant gran- ules	1	The exocrine cells contain a considerable amount of granules but less than in the other full-term cases	No granules dis- cernible		No granules dis- cernible	Rather abundant granules
	f	1	1				1
*)	A marked border of pepsinogen granules	Pepsinogen granules in rather many chief cells (Fig. 4)	A border of pepsinogen granules	Here and there small groups of pepsinogen granules	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible	Pepsinogen granules in rather many chief cells (Fig. 16)
	20	9	10	40.5	50 20	90 90	4 ∞
	4020	1930	4190	1400	1100	1140	2830
Hosp.	18. 1205/45 Karol. sjukh.	19. 666/45 Sachs' Hosp.	20. 689/45 Sachs' Hosp.	21. 717/45 Sachs' Hosp.	22. 721/45 Sachs' Hosp.	23. 723/45 Sachs' Hosp.	24. 742/45 Sachs' Hosp.

	Details of interest	1			1			
betv	erval in hours ween last meal and death	-	+	No food given	6.4	1	**	,
	Cause of death	Abortion Opera- tion	40 hours Congenital Debil.	Congenital Debil- ity	37 hours Pulmonary Ate. lectasis	Perforatio Capitis	48 bours Communital Dubil.	24 Congenital Debil- hours ity-Pulmonary Atelectasis
	Time of survival	٥	40 hours	<24 Conputer Appears Appears	37 hours	1	48 bours	>24 c
	Pro- teolytic activity	1	1	1	1	1		
Pancreas	Granules of the exocrine cells in the histological section	No granules dis- cernible (Fig. 34)	No granules dis- cernible	Incipient granule formation (Fig. 40)	More granules than in the pre- mature but less than in the full- term cases	Abundant coarse granules (Plate III)		
88	Peptic activ- ity	1	1	1	1	1	1	
Gastric Mucosa	Pepsinogen granules in the histological section of the mucosa	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible	Sparse pepsino- gen granules in single chief cells	Scattered groups of pepsinogen granules	A marked border of pepsinogen granules (Fig. 20)	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible
	Length in cm.	35	37	7	90	55	39.5	37
	Weight Length in g. in cm.	900	1200	1350	2870	3450	1630	1000
	Case No.	25. 2562/45 Allm. B.B.	26. 812/45 Sachs' Hosp.	27. 819/45 Sachs' Hosp.	28. 906/45 Sachs' Hosp.	29. 4812/45 Karol. sjukh.	30, 934/45 Sachs ² Hosp.	31. 994/45 Sachs

	i		No information concerning foe- tal age. The in- fant had a twin with a weight of 1340 g and a length of 41 cm.	1	The infant who was born at term had a twin with a weight of 3520 g and a length of 50 cm.	1
1	m		4	÷.	1	
24 Congenital Debil- hours ity+Pulmonary Atelectasis	26 hours Intracranial Hae- morrhage	Perforatio Capitis	7 hours Congenital Debil- ity+Pulmonary Atelectasis	48 hours Congenital Debil- ity	Asphyxia Asphyxia	Perforatio Capitis
> 24 hours	26 hours	1	7 hours	48 hours	0	
		1	1	1	1	1
		Abundant coarse granules	Granule formation just beginning	No granules dis- cernible	Abundant coarse granules (Fig. 49)	Abundant coarse granules (Fig. 37)
	1	1		-	1	1
No pepshogen granules dis- cernible	A marked border of pepsinogen granules	A marked border of pepsinogen granules (Fig. 7)	Single pepsino- gen granules	No pepsinogen granules dis- cernible	Amarked border of pepsinogen granules	A marked border of pepsinogen granules (Fig. 18)
100	57	70	39.5	1	œ	27
1000	1380	3680	1340	1740	0252	>3000
31. 994/45 Sachs' Hosp.	3281/45 Allm. B.B.	33. 4946/45 Karol. sjukh.	34. 18/46 Sachs' Hosp.	35. 42/46 Sachs' Hosp.	36. 845/46 Karol. sjukh.	37. 696/46 Söder- sjukh.

	interest							
	Details of interest	1	1	1	1			
	erval in hours ween last meal and death	31	p.,	m	co	*	m	No food
	Cause of death	5 hours Congenital Debil- ity+Pulmonary Atelectasis	24 hours Congenital Debil. ity	10 hours Congenital Debil- ity+Pulmonary Atelectasis+In- tracranial Hae- morrhage	-	Congenital Debil- ity	26 hours Intracranial Hac- monary Acces- tasis + Congeni- tal Debility	4 hours Erythroblastosis foetalis
	Time of survival	5 hours	24 hours	10 hours	<24 hours	14 hours	26 hours	4 hours
	Pro- teolytic activ- ity ²	1	1	1	1	1		
Pancreas	Granulos of the exocrine cells in the histological section	No granules dis- cernible	No granules dis- cernible	No granules dis- cernible (Fig. 44)	Rather abundant granules	No granules dis- cernible (Fig. 42)	No granules dis- cernible	i
88	Peptic activ- ity ¹	1	1	1		ï		
Gastric Mucosa	Pepsinogen granules in the histological section of the mucosa	Sparse pepsino- gen granules in single chief cells	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible	Sparse pepsino- gen granules in single chief cells	A border of pep- sinogen granules discernible	A marked border of pepsinogen granules (Fig. 5)
	Length in cm.	36.5	31	#	4	90	99	55
	Weight Length in g. in cm.	1510	750	1780	2400	1420	2430	0005
	Саме No.	38. 283/46 Sachs' Hosp.	39. 285/46 Sachs' Hosp.	40. 1057/46 Söder- sjukh.	41. 309/46 Sachs' Hosp.	42. 362/46 Sachs' Hosp.	43. 490/46 Sachs' Hosp.	44. 1305/46 Södersjukh.

		Whe infant who was born 8 weeks before calculated time had a twin with a weight of 1700 g and a length of 42 cm.	1	The infant who was born 5 weeks before calculated time had a twin with a weight of 1400 g and a length of 40.5 cm.		1
food	No food given	No food given	No food given	51	*	65
4 hours Erythroblastosis foetalis	1/2 hour Intrauterine As- phyxia+Supra- renal Apoplexy	I hour Congenital Debil- ity	<1/2 hour Intracranial Haemorrhage + Pulmonary Atelectasis	22 hours Congenital Debil. ity+Intra- cranial Haemor- rhage	36 hours Congenital Debil- ity+Intra- cranial Haemor- rhage	II hours Intrauterine As-
4 hours	1/2 hour	1 hour	<1/shour	22 hours	36 hours	II hours
		10.0				
1		I	1		7.8 No granules dis- cernible	ı
	+	1	1	10.0	00	5.
A marked border of pepsinogen granules (Fig. 5)	A marked border of pepsinogen granules (Fig. 26)	T	A marked border of pepsinogen granules	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible (Fig. 21)	A border of pep- sinogen granules
022	52.5	‡	90	7	36	20
4000	3070	2068	2920	1560	1020	3850
44. 1305/46 Södersjukh.	45. 3155/46 Karol. sjukh.	46. 3139/46 Karol. sjukh.	47. 3424/46 Söder- sjukh.	48. 954/46 Sachs' Hosp.	.19. 970/46 Sachs' Hosp.	50. 3069/46 Allm R R

tal Debility

Hosp.

¹ Expressed as in Fig. 28. ² Expressed as in Fig. 29.

	Details of interest		1	The infant who was born 10 weeks before calculated time had a twin with a weight of 1380 g and a length of 40 cm.	1		
Int	erval in hours ween last meal and death	86 10	No food given	No food given	?1	10	8
	Cause of death	29 hours Congenital Debil- ity	23 hours Congenital Debil. ity	3.5 hours Congenital Debil. ity	Congenital Debil- ity + Broncho- pneumonia (as- piration of am- niotic fluid)	Jours Conjectial Pebli ity, Palmonary Atchetasis	<24 Congenital Debil- hours ity+Pulmonary Atelectasis
	Time of survival	29 hours	23 hours	3.5 hours	3 days	s hours	> 54 hours
	Pro- teolytic activ- ity ³	1	1	1	1	S. S.	
Pancreas	Granules of the exocrine cells in the histological section		1	1	No granules dis- cernible (Fig. 30)		
25	Peptic activ- ity ¹	11.0	80°	90 90	19.1	21	z n
Gastrie Mucosa	Pepsinogen granules in the histological section of the mucosa	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible	No pepsinogen granules dis- cernible	Small groups of pepsinogen gra- nules (Fig. 10)	Pepsinogen gra- nules in single chief cells	No perpenden granules dis- cernible
	Length in cm.	80	21	90 60	44.5	=	ā.
	Weight Length in in g. cm.	820	700	1350	1790	1570	1000
	Case	51. 1040/46 Sachs' Hosp.	52. 1057/46 Sachs' Hosp.	53. 1092/46 Sachs' Hosp.	54. 1100/46 Sachs' Hosp.	55. 40/47 Sachs' Hosp.	64/47 Sachs' Hoen

		1		t	1	The infant who was born 8 weeks before calculated time had a twin with a weight of 1530 g and a length of 40 cm.
n	51	No food given	10	रा	1	6.
Congenital Debil- hours ity + Pulmonary Atelectasis	Congenital Debil- ity+Pulmonary. Atelectasis	Congenital Debil- ity + Intra- cranial Haemor- rhage + Supra- renal Apoplexy	48 hours Congenital Debil- ity + Intra- cranial Haemor- rhage	48 hours Congenital Debil- ity	Intracranial Haemorrhage + Pulmonary Ate- lectasis	9 hours Congenital Debil- ity + Intra- cranial Haemor- rhage
>24 hours	> 24 hours	>24 hours	48 hours	48 hours	=	9 hours
	9.0	10.0	4.60	1.0	61	-
		Rather abundant granules (Fig. 31)	1	No granules dis- cernible	ı	
r.	% 0	6.7	6.	0.6	38.6	21
No perpsinogen granules dis- cernible	No pepsinogen granules dis- cernible	A few pepsino- gen granules here and there (Fig. 9)	No pepsinogen granules dis- cernible (Fig. 6)	No pepsinogen granules dis- cernible (Fig. 11)	A marked border of pepsinogen granules (Fig. 23)	No pepsinogen granules dis- cernible
7	8	6.44	41	35	<u></u>	÷1
819690	880	9120	1780	920	3450	1780
64/47 Sachs' Hosp,	57. 73/47 Sachs' Hosp.	58. 127/47 Sachs' Hosp.	59. 121/47 Sachs' Hosp.	60. 140/47 Sachs' Hosp.	61. 700/47 Karol. sjukh.	62. 246/47 Sachs' Hosp.

¹ Expressed as in Fig. 28. ⁸ Expressed as in Fig. 29.

			Gastric Mucosa	18	Pancreas				bety	
Саве	Weight in g.	Weight Length in in g. g.	Pepsinogen granules in the histological section of the mucosa	Peptic activ- ity ¹	Granules of the exocrine cells in the histological section	Pro- teolytic activ- ity ⁸	Time of survival	Cause of death	erval in hours ween last meal and death	Details of interest
63. 252/47 Sachs' Hosp.	1660	66	Sparse pepsinogen granules in single chief cells (Fig. 14)	30 10	1	3.6	8 hours	8 hours Congenital Debil- ity+Pulmonary Atelectasis	No food given	I
64. 811/47 Allm. B.B.	1150	37	Sparse pepsino- gen granules in single chief cells (Fig. 22)	4:		2.0	5 days	Congenital Debil- ity	-	Ī
65. 327/47 Sachs' Hosp.	3055	20	A border of pep- sinogen granu- les	16.2	1	1	2 days	Pulmonary Atelectasis	3.5	1
66. 385/47 Sachs' Hosp.	3790	90	A marked border of pepsinogen granules (Fig. 13)	20.0	20.0 Abundant coarse granules	22.1	3 weeks	3 weeks Congenital Heart Disease	m	ħ.
67. 588/47 Sachs' Hosp.	2940	30	Pepsinogen granules in rather many chief cells	19.8		10.0	3 days	Intracranial Haemorrhage	3.5	t
68. 719/47 Sachs Hosp.	1310	33	No pepsinogen granules dis- cernible (Fig. 24)	11.8	1	0	< 24 hours	Congenital Debil- ity	No food given	
69. 3458/47 Allm. B.B.	1750	97	Small groups of pepsinogen granules	14.6	14.6 Kather abundant granules (Fig. 45)	17		Commo laste		
70. 768/47 Sachs	1250	330	gen granules in single chief	10.7	tion just begin- ning (Plate IV	2.5	7 hours	7 hours Congenital Debit- ity	food	

	The post mortem as late as 2.5 hours after death but specimen kept in cold.	1	1	1	Twins, born 10 weeks before	time.	1
Soor .	4 hours	1.5	No food given	→	ಣ	No food given	No food given
Congenital Debil- ity	3.6 31 hours Congenital Debil- 4 hours The post mortem ity + Intra- ranial Haemor- hours after death but sperimage cimen kept in cold.	3 weeks Congenital Debil- ity	5 hours Intracranial Hacmorrhage	26 hours Intracranial Haemorrhage	10 hours Congenital Debil- ity+Pulmonary Atelectasis	5 hours Congenital Debil- ity	5 hours Intracranial Haemorrhage
7 hours	31 hours	3 weeks	5 hours	26 hours	10 hours	5 hours	5 hours
io ei	9.6	1	65.3	15.5		6.0	18.1
tion just begin- ning (Plate IV Fig. 36)	ı	ı	I	1	ī	1	
10.7	51 51	9.6	18.0	11.3	9:	8.0	18.2
Sparse papsino- gen granules in single chief cells (Fig. 19)	Sparse pepsino- gen granules in single chief cells	I	1	1	L	1	
8	40	75	84	∞ ∞	30 60	45	55
20021	1720	1040	3200	2600	1200	920	3720
768/47 Sachs Hosp.	71. 902/47 Sachs' Hosp.	72. 996/47 Sachs' Hosp.	73. 92/48 Sachs' Hosp.	74. 112/48 Sachs' Hosp.	75. 143/48 Sachs' Hosp.	76. 144/48 Sachs' Hosp.	77. 729/48 Allm. B.B.

¹ Expressed as in Fig. 28. ³ Expressed as in Fig. 29.

	nterest				
	Details of interest	1	1	ì	1
bety	erval in hours ween last meal and death	*	No food given	1	0 -0
	Cause of death	34.4 24 hours Bronchopneumonia (aspiration of anniotic fluid)	<1 hour Congenital Debil- ity	Intrauterine As- phyxia	7.6 15 hours Congenital Debil- ity
	Time of survival	24 hours	<1 hour	o	15 hours
	Pro- teolytic activ- ity ²	4.46	1.3	52.4	7.6
Pancreas	Granules of the Pro- exocrine cells in teolytic the histological activ- section ity ²	1	1	1	1
38	Peptic activ. ity1	I	Ī	1	1
Gastrie Mucosa	Pepsinogen granules in the histological section of the mucosa	1	1		
	Length in	40	04	51	41
	Weight Length in in g. g.	3770	1550	3500	1570
	Case No.	78. 151/48 Sachs' Hosp.	79. 475/48 Södersjukh.	80, 649/48 Södersjukh.	81. 185/48 Sach's Hosp.

² Expressed as in Fig. 29. ¹ Expressed as in Fig. 28.

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ACTA PÆDIATRICA





ÜBER DIE EINWIRKUNG DER KÄLTE AUF DAS PERIPHERE BLUTBILD DES SÄUGLINGS

EXPERIMENTELLE UNTERSUCHUNGEN

VON

ELISABETH MAASIK

AKADEMISCHE ABHANDLUNG

ACTA PÆDIATRICA VOL. XXXV SUPPLEMENTUM VII 1948

Helsingfors 1948 Frenckellska Tryckeri Aktiebolaget. Vo

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VORWORT.

Das Thema der vorliegenden Arbeit wurde mir von meinem hochverehrten Lehrer, dem Direktor der Universitäts-Kinder-klinik, Herrn Professor Dr. med. Arvo Ylppö, gegeben.

Mit ausserordentlichem Wohlwollen und Interesse hat er die Arbeit verfolgt und durch seine reiche Erfahrung, ohne Mühe und Zeit zu sparen, fortlaufend angeleitet.

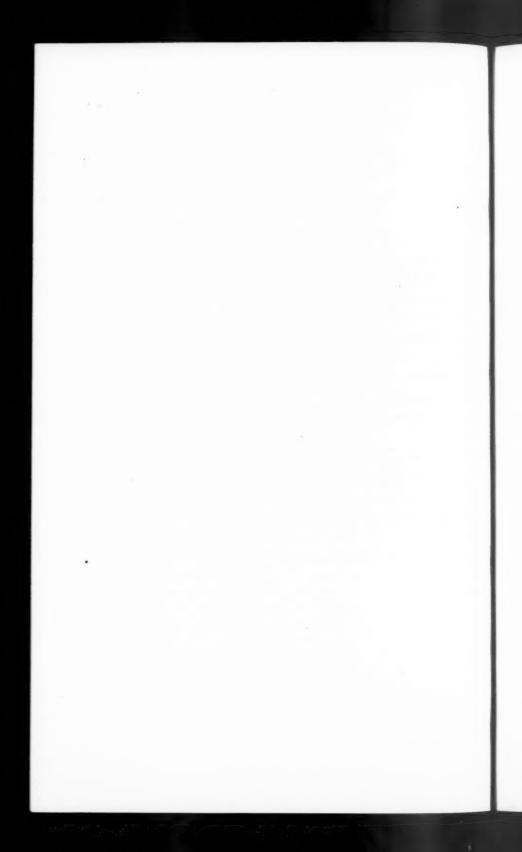
Für die Bereitwilligkeit, die Prof. Dr. med. A. Ylppö meiner Arbeit entgegengebracht hat, sowie für seine wertvollen Ratschläge, spreche ich meinen ehrerbietigsten und herzlichsten Dank aus.

Den Ärzten und Schwestern der Kinderklinik danke ich herzlich für ihre Hilfsbereitschaft und ihr Entgegenkommen.

Für die mir gewährte ökonomische Unterstützung aus dem Pädiatrischen Forschungsfond spreche ich meinen ergebensten Dank aus.

Helsingfors, im September 1948.

Die Verfasserin.



EINLEITUNG.

Über die Einwirkung thermischer Reize, insbesondere der Kälte, auf das periphere Blutbild, sind wenige und verhältnismässig unvollständige Untersuchungen ausgeführt worden.

Die Einwirkung der Kälte auf das Blutbild des Säuglings ist unerforscht, dagegen haben mehrere Autoren Arbeiten über den Einfluss warmer Bäder, künstlich erzeugten Fiebers usw. auf das Blutbild des Säuglings veröffentlicht.

Es war mein Bestreben, mit Hilfe von Experimenten, die Einwirkung der Kälte auf das Blutbild des Säuglings näher aufzuklären.

Als Einleitung der vorliegenden Arbeit stellte ich Versuche mit Meerschweinchen an.

An Säuglingen untersuchte ich folgendes:

- 1) Die Einwirkung kalter Vollbäder auf das periphere Blutbild.
- 2) Die Einwirkung lokalen Kältereizes, hervorgerufen durch kalte Fussbäder, auf das periphere Blutbild.
- 2) Die Einwirkung zugeführter kalter Milch resp. kalten Bariumbreies auf das periphere Blutbild.

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LITERATURÜBERSICHT.

Über die sowohl physiologischen als auch durch verschiedene Einflüsse bedingten Veränderungen des Blutbildes sind zahlreiche Arbeiten veröffentlicht worden.

Die Anschauungen der einzelnen Forscher sind stark divergierend und stehen oft in direktem Gegensatz zu einander.

Nach GLANZMANN (1941) befindet sich offenbar in der Gegend des III. Ventricels ein vegetatives Nervenzentrum, welches das Blutbild regelt.

Auch Hoff ist der Ansicht, dass das Blutbild über vegetative Zentren des Gehirnes geregelt wird. Die vegetativen Zentren stehen in Wechselbeziehung zu den endokrinen Drüsen und damit zu den Hormonen.

Nach GLASER (1922) beruht die Kontraktion der Gefässe auf Reizung des Sympathicus, da bekanntlich im letzteren die gefässverengernden Nervenfasern verlaufen. Besteht ein Übergewicht im Vagusgebiet, kann sich dieser Gefässreflex nicht ausbilden, es kommt nicht zu einer Verengung, sondern im Gegensatz zu einer Erweiterung der Gefässe.

Bei vagotonischen Zuständen erweitern sich die oberflächlichen Hautgefässe.

GLASER ist der Ansicht, dass sich die physiologischen Veränderungen des Blutbildes, die Schwankungen der Blutkörperschenzahl, durch Vasodilatation und Vasokonstriktion erklären lassen. HOFF und SIEVERS (1924) sehen es als unwahrscheinlich an, dass die Zahl der Blutzellen nur von physikalischen Strömungsbedingungen und vom Gefässtonus abhängen soll.

DENNING behauptet, dass alle ausgedehnten, die ganze Körperoberfläche betreffenden vasomotorischen Vorgänge auf dem Wege über höhergelegene vasomotorische Zentren vorsichgehen. Nach HINTZE (1922) sind die Kapillaren einer von den Nerven unabhängigen Kontraktion fähig.

EBBECKE (1917) ist der Ansicht, dass die Verengung und Erweiterung der Kapillaren eine selbständige, zuweilen der arterischen Gefässverengung entgegengesetzte Tätigkeit der Kapillarwand ist.

Die meisten Forscher meinen, dass die Schwankungen des Blutbildes durch Veränderungen der Gefässweite bedingt sind.

MÜLLER behauptet, dass die Änderungen der Gefässweite durch die vegetativen Nerven geregelt werden.

Die Schwankungen der Leukozytenzahl sind am meisten erforscht worden, wogegen auf die Erythrozytenwerte kein so grosses Gewicht gelegt worden ist.

GLASER (1922) hat als erster behauptet, dass die Erytrozytenund Leukozytenkurve analog verlaufen.

VEJLENS hat 1938 eine ausführliche Arbeit veröffentlicht. Nach seiner Ansicht ist der Mechanismus für die Verteilung der weissen Blutkörperchen im Blutgefässsystem an die parakapillaren Gefässe gebunden. Eine Veränderung der Verteilung der weissen Blutkörperchen bedeutet, dass Pseudoleukozytosen oder Leukopenien entstehen, oder dass eine grössere oder geringere Anzahl weisser Blutkörperchen aus einem Blutgefässgebiet in ein anderes übergeführt werden. Veränderungen der Gefässweite innehalb der Dimensionen der parakapillaren Blutgefässe, etwa 0,300—0,020 mm, und eine Veränderung der Gefässweite, die eine Zunahme oder Abnahme der Anzahl der parakapillaren Blutgefässe verursachen, führen zu Verschiebungen sowohl der roten, wie auch der weissen Blutkörperchen. Nach Vejlens werden die weissen Blutkörperchen mehr als die roten betroffen.

Alle physiologischen und pathologischen Prozesse, die die Strömungsgeschwindigkeit in den parakapillaren Venen verändern, wirken auf die Verteilung der weissen Blutkörperchen im Blutgefässsystem ein.

Nach Petersen, Hölscher, Müller besteht bei der Verteilung der Leukozyten ein splanchnoperipheres Gleichgewicht. Bei peripherer Leukopenie sieht man hohe Leukozytenwerte in der Leber, Milz und in den Splanchnicus Blutgefässen.

Bevor ich näher auf die durch thermische Reize verursachten Blutbildveränderungen eingehe, will ich in Kürze die Anschauungen einiger Forscher über physiologische Blutbildveränderungen erwähnen; ausserdem führe ich einige Beispiele an über die Einwirkung nahe dem physiologischen liegender und anderer Reize auf das Blutbild.

Die deutlichsten physiologischen Blutbildschwankungen sieht man beim Neugeborenen und Säugling.

Nach v. Pfaundler sind die Erythrozytenwerte des Neugeborenen 5—7 Mill. pro cmm Blut, die Hämoglobinwerte sind 110—130 % Sahli.

Nach Benjamin sieht man die höchsten postnatalen Erythrozytenwerte am 2. Lebenstage.

In der Neugeburtperiode erfolgt eine physiologische Senkung der Erythrozyten- und Hämoglobinwerte.

Nach Holt, Washburn u. a. ist das Minimum der Blutwerte beim ausgetragenen Kinde gewöhnlich in der 6.—9. Lebenswoche erreicht. Unter optimalen Verhältnissen sinken die Erythrozytenwerte auf c:a 4 Mill., ein Absinken auf 3 Mill. ist nicht ungewöhnlich (Holt). Beim Frühgeborenen sind die Erythrozyten- und Hämoglobinwerte nach der Geburt höher als beim ausgetragenen Kinde. Das postnatale Absinken ist gewöhnlich ausgesprochener. (Holt).

Lichtenstein behauptet, dass die Hämoglobin- u. Erythrozytenwerte im Grossen und Ganzen mit denen ausgetragener Kinder übereinstimmen.

Die Angaben über die Leukozytenwerte normal ausgetragener Kinder sind sehr variierend.

Nach LIPPMAN ist die Anzahl der Leukozyten sofort nach der Geburt 16 000 und steigt im Laufe der ersten 12 St. auf 22 500, am 5. Lebenstag ist die Anzahl auf 9 500 abgesunken.

Nach HOLT findet man beim Neugeborenen gewöhnlich eine polymorphonucleäre Leukozytosis mit Werten 15 000—30 000.

Für normale Leukozytenwerte des Säuglings geben KARNITZKI 8 600—16 000, ROMINGER 9 000—23 700, SMITH 6 000—16 000 und WASHBURN 8 000—16 500 an.

Starke Schwankungen finden von Tag zu Tag statt. Die Variationen sind grösser als die der Erythrozyten- und Hämoglobinwerte. Die Leukozytewerte können sich im Laufe von wenigen Stunden bis um 100 % ändern. Bei jungen Kindern folgt die Leukozytenkurve der Lymphozytenkurve.

Das Differentialblutbild weist beim ausgetragenen Neugeborenen in den ersten Lebenstagen eine starke Linksverschiebung auf, die in wenigen Tagen schwindet.

Nach Fletcher und Mitchel (1927) finden starke Schwankungen des Differentialblutbildes im Laufe eines Tages statt.

Nach Holt findet man bei ausgetragenen Kindern selten Myelozyten nach dem ersten Lebenstage.

Die Menge der Erythroblasten ist der Reife des Neugeborenen umgekehrt proportional (Landé).

Nach Holt besteht im normalen Blutbild des Neugeborenen gewöhnlich eine Lymphozytosis mit 60—70 % der weissen Blutzellen.

Nach Lippman (1924) sind basophile Zellen beim Neugeborenen selten.

Die Eosinophilen fehlen nach LANDÉ oft völlig.

WASHBURN (1941) gibt für das Differentialblutbild des Säuglings folgende Werte an:

Basophile 0—5 %, Eosinophile 0—7 %, Neutrophile 5—55 %, Stabkernige 0—9,5 %, Segmentkernige 5—49 %, Juvenile 0—2 %, Monozyten 0—16 %, Lymphozyten 42,5—90,5 %.

Nach Washburn rufen Körperbewegung, Temperaturveränderungen des Körpers, Schlaf u. Bad Veränderungen des Blutbildes hervor.

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Nach AITKEN haben die Umgebungstemperatur, Tageszeit, Gewicht und Muskelarbeit keinen Einfluss auf die Leukozytenanzahl.

Über das Verhalten der Leukozyten des Säuglings bei der Verdauung sind die Ansichten auch verschieden. Schiff und Stransky sehen eine Verdauungsleukopenie für physiologisch an. Nach Hainiss und Heller (1924) wechseln eine Verdauungsleukozytose und Verdauungsleukopenie regellos in der Neugeburtszeit, um an ihrem Ende in eine regelmässig auftretende Leukozytose überzugehen.

JACOTTET konnte bei Brustkindern keine Verdauungsleukozytose feststellen, sieht die Muttermilch als physiologische Nahrung an. Es können jedoch Blutbildveränderungen vorkommen,

die die Fehlergrenze überschreiten. Fletcher al. Mitchel. halten die Verdauungsleukozytose für unkonstant.

Die Anschauungen über physiologische Blutbildschwankungen beim Erwachsenen sind sehr variierend.

VAN DEN BERGHE (1946) behauptet, dass im Laufe eines Tages Leukozytenschwankungen um 201 ⁰/₀ vorkommen. Auch GOUBERGITZ (1941) ist derselben Ansicht.

Über den Einfluss der Verdauung sind viele Arbeiten veröffentlicht worden. Nach MÜLLER, E. F. (1922) findet eine Senkung der Leukozytenzahl nach jeder physiologischen Magenerweiterung statt. Er behauptet, dass eine gemeinsame Reaktion der Peripherie und des Splanchnicunsgebietes vorhanden ist. GLASER (1922) ist der Ansicht, dass der verschiedene Ausfall der Leukozytenreaktion nach demselben Nahrungsreiz dafür spricht, dass an verschiedenen Tagen ein differentes Verhalten des Tonuszustandes des vegetativen Nervensystems vorhanden ist, so dass z.B. an einem Tage nach Milchaufnahme eine vagotonische Leukozytose entsteht. Befindet sich das vegetative Nervensystem in einer relativen Ruhelage, so bringt der Nahrungsreiz überhaupt keine Verteilungsreaktion der Leukozyten zustande.

Nach Scheunert und Krzyvanek (1926) rufen Schreck und andere psychische Erregungszustände eine Verminderung der Blutkörperchenmenge hervor, die innerhalb weniger Minuten abklingt.

Unspezifische Reize.

Walthöfer (1927) stellte fest, dass ein nahe dem Physiologischen liegender Reiz recht starke Schwankungen der Erythrozyten-, Hämoglobin- und Leukozytenwerte verursacht. Als Reiz benutzte er den Einstich mit der Francke'schen Nadel ins Ohrläppchen. Gleich nach dem Einstich stellte er ein bedeutendes Absinken der obenerwähnten Blutwerte fest, das ca 10 Min. anhielt, worauf ein Ansteigen erfolgte. Walthöfer empfielt daher den Ausdruck »Konzentrationsleukozytose», statt »Verschiebungsleukozytose» zu gebrauchen, da die corpus-

culären Elemente des Blutes bei durch Vasomotorentätigkeit hervorgerufenen Vorgängen unberührt bleiben, die Blutflüssigkeit allein ist in stetem Aus- und Rückfliessen durch die Kapillarwand begriffen, wodurch die Blutwerte erhöht und erniedrigt werden.

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MÜLLER E. F. (1923) stellte fest, dass intracutane Injectionen physiologischer Kochsalzlösung auf das gesamte Blutgefässgebiet des Körpers einwirken. Als Folge des Reizes tritt eine Verengung der Hautgefässe mit Leukopenie und eine Erweiterung der Splanchnicusgefässe mit Leukozytose ein.

Nach Filinski (1925) findet bei elektrischer Reizung des Vagus beim Hunde eine Leukopenie in den Gefässen des Ohres und eine Leukozytose in den Mesenterialgefässen statt. Die Veränderung der Leukozytenanzahl trat sehr rasch auf und verschwand ungefär i ½ Min. nach Aufhören des Reizes. Die Erscheinungen erwiesen sich als unabhängig vom Gefässtonus und der Einwirkung der Nebenniere. Filinski nimmt an, dass es sich eventuell um Veränderungen des K-Ca Gleichgewichtes handelt.

GERMAN (1939) stellte fest, dass bei Reizung der peripheren Abschnitte des vegetativen Nervensystems im Halsanteil beim Pferde folgende Veränderungen eintreten:

Vagusreizung verursacht eine Abnahme der Viskosität des Blutes, eine Vermehrung der Anzahl der Eosinophilen und Leukozyten.

Sympathicusreizung verursacht eine Zunahme der Segmentkernigen und Monozyten samt eine geringe Verminderung der Leukozyten und Eosinophilen. Die Viskosität des Blutes nimmt zu. Die Resistenz der Erythrozyten verändert sich.

BÜRKER stellte fest, dass Vagusreizung zu einer Anhäufung der Leukozyten in den inneren Organen und Abnahme in der Peripherie führt, Sympathicusreizung hat umgekehrte Wirkung. HORTLING (1948) behauptet, dass eine neurovegetative Regulation der Leukozytenregeneration beim Menschen denkbar ist.

MUTO, TAKAHASHI, NIRAOKA nehmen an, dass der Reiz des Nervensystems sich auf Umwegen über die Leber, die dann Stoffe ausschüttet, die die Leukozytose anregen (Neutrophilin), auswirkt. Gottsegen konnte im Blutplasma vom Kaninchen Leukopoietine nachweisen, die auf die Leukozytenregulation einwirken.

Über die Bedeutung der Nebenniere bei Reizen.

SELVE (1937) hat festgestellt, dass reizende schädliche Einflüsse, wie Kälte, traumatische Schäden, akute Infektionen usw. im Körper eine Verteidigungsreaktion hervorrufen. Es ist unbekannt, ob der Reiz auf dem Blutwege oder über das Nervensystem wirkt.

Selve unterscheidet 3 Stadien: 1. Stadium des Alarmes. 2. Stadium der Resistenz. 3. Stadium der Exhaustion.

Selve führte Versuche mit Ratten aus. 6—48 St. nach dem Schaden fand er weitgehende Veränderungen im Organismus der Versuchstiere. Abnahme der Milz- u. Thymusgrösse, peritoneale und pleurale Exudate, Erosionen im Verdauungstrakt, Absinken der Körpertemperatur.

Die Veränderungen der Nebennieren waren besonders gross. Es findet eine Hyperplasie der Nebennierenrinde statt. Die corticalen Lipoide und Granulas des Markes nehmen ab.

Selve stellte fest, dass die Kälte ein besonders aktiver Faktor ist.

Selve betrachtet als eine der wichtigsten Aufgaben der Nebennieren, bei schädlichen Einflüssen eine Anpassung herzustellen. Cannon (1925) stellte fest, dass es endgültig bewiesen ist, dass das Nebennierenmark unter bestimmten Bedingungen bei Reizen reflektorisch erhöhte Mengen Adrenalin an das Blut abgibt, die zu beträchtlichen Wirkungen ausreichen.

CANNON und QUERIDO (1925) fanden, dass bei starkem Wärmeverlust eine gesteigerte Adrenalinausscheidung stattfindet, um den Körper vor Unterkühlung zu schützen. Sie sehen sowohl die Nebennierenrinde als auch das Mark bei der Wärmeregulation für bedeutsam an, das Mark ist jedoch zur Konstanthaltung der Temperatur entbehrlich.

HARTMAN, BROWNELL, CROSBY (1918) fanden in der Nebenniere von Versuchstieren, die der Kälte ausgesetzt waren, his-

tologische Veränderungen, die auf eine gesteigerte hormonale Funktion deuten. Sie nehmen an, dass es sich um eine gesteigerte Adrenalinausschüttung handelt.

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DALTON und SELVE (1939) stellten Versuche an, um festzustellen, wie die Alarmreaktion auf das Blutbild einwirkt. Als Versuchstiere benutzten sie Ratten und Mäuse. Sie erkannten, dass während der Alarmreaktion Veränderungen des Blutbildes stattfinden. Man sieht eine polymorphonucleare Leukozytosis. Die hämatologischen Veränderungen sind die gleichen bei beiden Geschlechtern.

DALTON und SELVE wandten als Reiz Formaldehyd und körperliche Anstrengung an.

Im Blutbild findet erst ein vorübergehender Abfall der Leukozyten statt, worauf eine neutrophile Leukozytosis erfolgt. 30 Stunden nach der Formaldehyd-Injektion waren die Ausgangswerte wieder erreicht.

Sie stellten fest, dass bei der durch körperliche Anstrengung hervorgerufenen Alarmreaktion eine Abnahme der Erythrozytenzahl ohne Hämokonzentration stattfindet.

Selve behauptet, dass Kälte ein Stimulus sei, der einen unkomplizierten Typus der Alarmreaktion hervorruft.

Tyslowitz und Ashwood (1942) stellten fest, dass 70—90 g wiegende hypophysektomierte Ratten ihre Körpertemperatur bei einer Umgebungstemperatur von 0° C nicht aufrecht zu halten vermögen.

Pituitrin- und Corticotrophinextrakte steigern die Resistenz, wenn sie in Perioden von 1 St. — 14 Tagen gegeben werden. Diese Extrakte waren uneffektiv, wenn die Nebennieren entfernt waren, jedoch wirksam nach Thyreoidektomie.

Thermische Reize.

Nach THAUER (1939) befindet sich das Wärmezentrum im Hypothalamus. Thermische Beeinflussung des Hirnstammes ruft tiefgehende Veränderungen im Wärmehaushalt hervor.

ISENSCHMID nimmt an, dass auch die Gehirnrinde die Wärmeregulation beeinflussen kann.

Nach Aronson, Sachs, Isenschmid findet die Wärmeregulation über das im Tuber einerum liegende sympathische und parasympathische Nervenzentrum statt.

DELESTRE, HAHN, v. PAUNDLER sind der Ansicht, dass durch die mangelhafte Entwicklung des Zentralnervensystems das Wärmezentrum des Frühgeborenen noch nicht imstande ist, Gleichgewicht zwischen Wärmeproduktion und Wärmeabgabe zu halten.

Ylppö u. a. sehen als Ursache der Temperaturschwankungen des Frühgeborenen die mangelhafte Ausbildung des subcutanen Fettgewebes, die relative Grösse der Körperoberfläche im Vergleich zum Körpergewicht an. Nach Ylppö können Temperaturschwankungen der Frühgeburten oft durch intracraniale Blutungen verursacht sein, obgleich man bei diesen Fällen eine konstante Umgebungstemperatur aufrecht hält.

Bei wechselnder Umgebungstemperatur erfolgt die Regulierung der Körpertemperatur durch Anpassung der Wärmebildung an den Bedarf, sowie durch Veränderung der Wärmeabgabe (ECKSTEIN).

Nach Eckstein (1926) ist die chemische Wärmebildung der Frühgeburten normal entwickelt.

Nach Isenschmid sinkt und steigt die Körpertemperatur beim Erwachsenen bei der calorimetrischen Veränderung der Aussenluft.

Lundgren (1947) führte Versuche aus zur Feststellung, welche Einwirkung die »finnische Sauna» auf die Rektaltemperatur erwachsener Männer habe. Nach einem Aufenthalt von 5 Min. in der »Sauna» stieg die Rektaltemperatur, ½ St. nach dem Bade war die Ausgangstemperatur wieder erreicht.

Liebemeister stellte fest, dass das Trinken grosser Mengen kalten Wassers die Körpertemperatur sinken lässt.

Hill (1937) behauptet, dass lokale Kälteapplikation die Körpertemperatur senkt.

Zahlreiche Forscher haben den Einfluss thermischer Reize, hauptsächlich warmer und kalter Bäder, auf das Blutgefässsystem und Blutbild beschrieben.

Unter identischen Bedingungen beobachteten die verschiedenen Forscher sehr divergierende und oft direkt entgegenge-

setzte Veränderungen. Tholezan, Brown, Sequard haben festgestellt, dass selbst bei streng lokalem Wärmeentzug, oder bei Wärmezufuhr, die Vasokonstriktion oder Vasodilatation nicht allein auf das dem thermischen Reiz ausgesetzte Hautgebiet beschränkt bleibt, sondern die ganze Körperhälfte gleicherweise reagiert. Diese »konsensuelle Reaktion» ist ihrer Ansicht nach in beschränktem Masse auch auf der inneren Oberfläche des Körpers, z.B. an den Gefässen der Magen- und Darmschleimhaut, feststellbar.

Aldenhoven nimmt an, dass die Erwärmung der Magenschleimhaut eine Änderung der Hauttemperatur verursacht, so dass eine funktionelle Koppelung zwischen den Gefässgebieten der Haut und der Schleimhaut des Magen-Darmkanals angenommen werden muss.

HERLITZ (1943) führte Versuche mit Neugeborenen aus und untersuchte die konsensuelle Kältereaktion der Hautgefässgebiete der Stirn und des Unterarmes.

Er stellte fest, dass die konsensuelle Hautgefässreaktion auf Kälte beim Neugeborenen in der Regel fehlt, oder noch nicht ausgebildet ist, so dass sie durch Veränderungen der Hauttemperatur wie beim Erwachsenen, nicht nachgewiesen werden kann.

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HERTZMAN und ROTH (1942) haben die Reaktion der Blutgefässe bei lokaler Kälteeinwirkung studiert und kamen zum Resultat, dass bei lokaler Kälteeinwirkung erst eine initiale Konstriktion, nach 5—16 Min. eine Dilatation der Hautblutgefässe erfolgt. Die Dauer ist verschieden. Nach der Dilatation tritt wiederum eine Konstriktion ein. Ähnliche Veränderungen konnten sie im Kontrollfinger derselben oder anderen Hand feststellen. Sie sind der Ansicht, dass durch Kälte erweckte vasomotore Reflexe die initiale Konstriktion im Versuchs- und Kontrollfinger, im letzteren nicht so stark, verursachen. Die reaktive Konstriktion nach der Dilatation kann auch im Kontrollfinger erfolgen.

CHIN (1935) stellte Versuche mit Fröschen an. Bei Abkühlung des Blutserums auf $+20^{\circ}$ C fand eine Dilatation, bei höheren oder niedrigeren Temperaturen des Serums fand eine Konstriktion statt.

ATZLER erkannte, dass die Konstriktoren sich durch Abkühlung oder Erwärmung leichter blockieren lassen als die Dilatatoren.

Nach Ebbecke kontrahieren die Arteriolen und Kapillaren reflektorisch beim Eintauchen eines Armes in kaltes Wasser. Beim Wiederholen des Versuches am abgebundenen Arm rötet sich der eingetauchte Hautbezirk lebhaft arteriell. Die Rötung der Haut besagt, dass die Kapillaren erweitert sind. Der arterielle Farbton ist durch die geringe Stoffwechselintensität im abgekühlten Arm bedingt, so dass das arterielle Blut arteriell bliebt.

Es handelt sich nicht um einen reflektorischen Vorgang, sondern um eine lokale Einwirkung der Kälte. Eine derartige Wirkung lässt sich nur durch sehr hohe oder sehr geringe Temperaturen erzielen.

Nach CARRIER sind die Kapillaren im warmen Bad weit, bei $+20^{\circ}$ C teilweise kontrahiert, es entwickeln sich Stasen. Bei $+10^{\circ}$ C erschlaffen die Kapillaren und füllen sich teilweise mit Blut.

Rous ist der Ansicht, dass bei Hautreizen in der Haut histaminähnliche Stoffe frei werden, die eine Dilatation der Kapillaren hervorrufen.

Nach Gollwitz, Meyer, Bingel verursachen warme Bäder eine Ausscheidung acetylcholinartiger Substanzen, die einen erweiternden Einfluss auf die subcutanen Arteriolen haben.

WINTERNITZ (1893) legte dar, dass allgemeine den ganzen Körper treffende thermische Reize, wie kalte Abreibungen, kalte Duschen, Vollbäder und auch wechselwarme Prozeduren, mit seltener Ausnahme eine Vermehrung der weissen und roten Blutkörperchen, sowie eine Zunahme des Hämoglobingehaltes, verursachen.

Die maximale Zunahme der Ery betrug I 860 000, die der Leukozyten fast das dreifache der Anzahl vor dem Versuche. Die Zunahme des Hämoglobingehaltes betrug maximal 14 %.

Das Maximum der Zunahme trat in den meisten Fällen erst I Stunde nach der thermischen Einwirkung ein. WINTERNITZ konnte oft eine Zunahme der Leukozyten erst nach einer Wiederabnahme der Erythrozyten beobachten. Die Veränderung der Blutzusammensetzung hielt verschieden lange Zeit an, nach 2 Stunden konnte er meistens bei beiden Zellarten wieder eine Abnahme feststellen. Die Vermehrung der Leukozyten war weniger konstant. In seltenen Fällen, bei denen die Leukozyten eine deutliche Zunahme aufwiesen, wurden nach dem Versuch absolut und relativ weniger Leukozyten gefunden.

In Fällen, bei denen eine Abnahme der Erythrozyten stattfand, erfolgte jedoch eine Zunahme der Leukozyten.

WINTERNITZ sieht als Ursache der veränderten Zusammensetzung des Blutes eine Veränderung der Zirkulation, Hetzaktion und dem Tonus der Gefässe und des Gewebes an, die durch die Kälteeinwirkung hervorgerufen werden.

WINTERNITZ nahm an, dass die Zirkulationsverhältnisse günstiger werden, und dadurch aus den verschiedenen Geweben und Organen die dort stagnierten Zellen dem allgemeinen Kreislauf zugeführt werden.

KNÖPFELMACHER (1893) stellte konstant nach kalten Bädern eine Zunahme der Erythrozyten um fast 30 % fest. Die Leukozytenzahl stieg in den meisten Fällen mehr als die der Erythrozyten. Die Veränderungen der Erythrozyten- und Leukozytenwerte erwiesen sich als vorübergehend. In den meisten Fällen fand nach ½ St. wieder ein Absinken statt.

KNÖPFELMACHER sieht als Ursache eine durch den Kältereiz bedingte Veränderung der Verteilung der Blutzellen an.

Breitenstein (1896) konnte bei Typhösen und Rekonvaleszenten auch eine Vermehrung der Erythrozyten nach kalten Bädern feststellen.

Nach Friedländer findet nach anhaltender Kälteeinwirkung eine Abnahme der Erythrozytenwerte, mit gleichzeitiger Vermehrung der Leukozytenwerte, statt.

REINEBOTH und KOHLHARDT (1899) führten Versuche mit Kaninchen aus. Sie kühlten die Tiere und 10—15° ihrer Körpertemperatur ab. Sie erzielten es durch Eintauchen in 1—3° R kaltes Eiswasser während einer Dauer von 5 Min.

In den meisten Fällen fand eine mässige Verminderung des Erythrozytengehaltes mit gleichzeitiger bedeutender Verringerung des Hämoglobingehaltes statt. Bei wiederholtem starken Abkühlen fand eine erhebliche Verringerung der Erythrozytenwerte statt. Reineboth und Kohlhardt sehen eine Schädigung der kreisenden Blutzellen als Ursache der Veränderung an. Durch die Kälteeinwirkung tritt eine Hämoglobinämie ein, die anfangs hauptsächlich durch einen Hämoglobinverlust der Zellen, später auch durch Untergang von Erythrozyten zustande kommt.

BECKER (1901) führte Untersuchungen über die Veränderungen des Kapillar- und Venenblutes bei Gesunden und leicht Kranken aus. Die Versuchspersonen wurden für 4 Minuten einer 7—16° R Dusche ausgesetzt, in anderen Fällen gab man den Versuchspersonen für 15 Min. 20°—30° warme Bäder. Die Erythrozytenwerte stiegen bei fast allen Fällen sofort nach dem Kältereiz, die Leukozytenwerte sanken, maximal um 122 %.

BECKER konnte keinen konstanten Unterschied in der Blutzellenanzahl der Venen und Kapillaren feststellen.

Nach I Stunde hatten die Erythrozytenwerte wieder abgenommen, meistens konnte auch eine Abnahme gegenüber der vor der Dusche gefundenen Werte festgestellt werden.

BECKER nimmt als Ursache der Veränderung eine veränderte vasomotorische Beeinflussung, eine Wasserabgabe des Blutes und zu einem geringen Teil auch eine Stauung der Blutkörperchen in den Kapillaren an.

BAZETT (1925) fand, dass Bäder mit einer T° von 37—37° C beim Erwachsenen im venösen Blut erst ein Absinken, dann ein Steigen des Hämoglobingehaltes verursachen. Das Blut wurde der Cubitalvene entnommen.

Barbou und Mitarbeiter haben festgestellt, dass Abkühlung und Erwärmung den Wassergehalt des Blutes verändern.

Nach Barcroft und Mitarbeiter nimmt die Gesamtblutmenge bei Kälteeinwirkung ab. Die Organe bzw. Gewebe, in denen das Wasser sich ansammelt, sind noch nicht bekannt. Das Blut wird bei Kälteeinwirkung durch Kontraktion der Gefässe aus der Peripherie verdrängt.

Wertheimer, nimmt an, dass durch Kälteeinwirkung eine Erweiterung der Blutgefässe der Muskeln stattfindet.

GLASER (1922) behauptet, dass sich bei der Verengung der Blutgefässe eine Verteilungsleukozytose ausbildet, gleichzeitig findet eine Zunahme der Erythrozytenzahl statt. Die Kontraktion der Gefässe beruht auf einer Reizung des Sympathicus, falls ein Übergewicht im Vagusgebiet besteht, kommt es zu einer vagotonischen Leukopenie. Bei vagotonischen Zuständen erweitern sich die oberflächlichen Hautgefässe.

Nach de la Grande y Vegas findet bei Kindern im Alter von 9—14 J. nach Handbädern, — erst 5 Min, im Handbad mit einer Wassertemperatur von 10° C, worauf nach 3 Min. ein Handbad von + 50° C gegeben wurde, — nach der Exwärmung eine relative Vermehrung der Lymphozyten und Monozyten statt. Falls bereits eine Lymphozytose und Neutropenie bestanden hatten, kam es zu einer Zunahme der Monozyten und in geringem Grade der Neutrophilen. Bei bereits bestehender Neutrophilie fand eine relative Verminderung der Neutrophilen und Zunahme der Monozyten statt, die Lymphozytenwerte veränderten sich nicht.

NEDZEL kühlte Hunde mit Eispackungen ab und stellte ein Absinken der Leukozytenwerte, sowohl in den Tracheal-wie auch den Ohrkapillaren, fest.

Nach Arneth verursachen heisse und kalte Bäder eine Steigerung des Stoffwechsels mit Leukozytose.

Nach Davidov findet beim Eintauchen einer Hand für 2 Min. in ein Wasserbad von 40—42° C reflektorisch in der auderen Hand erst eine Leukopenie und dann eine Leukozytose statt.

Nach FALUDI (1938) verursachen lokale thermische Reize keine Veränderung des Blutbildes. Weder nach kalten noch warmen Handbädern konnte er Veränderungen der Leukozytenwerte feststellen.

KIJANEN und HIETARANTA (1930) untersuchten die Einwirkung warmer Bäder auf die Körpertemperatur und die Anzahl der weissen Blutkörperchen des Frühgeborenen. Es fand stets ein Temperaturanstieg statt. Sie stellten sowohl eine Leukozytose als auch eine Leukopenie fest.

In Versuchen über das Einwirken künstlich erzeugtem Fiebers beim Säugling, das durch heisse Bäder (40-41° C) hervor-

gerufen wurde, stellte MAASIK (1945) fest, dass im Blutbild folgende Veränderungen stattfanden: die Leukozytenwerte stiegen in sämtlichen Fällen, zwar nicht bei allen in gleich starkem Masse, gleichzeitig sanken die Erythrozytenwerte in allen Fällen. In fast allen Fällen sah man im Differentialblutbild eine Linksverschiebung. Die Lymphozyten nahmen ab.

Ungefähr I Stunde nach dem Bade hatten die Erythrozyten annähernd ihre Ausgangswerte erreicht. Auch die Leukozytenwerte waren in den meisten Fällen im Absinken. Das Differentialblutbild wies annähernd dieselben Werte wie vor dem Bade auf.

Gemeinsam mit Petersen führte Müller, E. F. Versuche aus, um festzustellen, welche Einwirkung das Trinken von kaltem und warmem Wasser auf das Blutbild habe. Sie stellten fest, dass das Trinken von warmem Wasser eine Abnahme der Leukozytenwerte der Peripherie verursacht. Kaltes Wasser hatte eine umgekehrte Wirkung.

Nach MÜLLER, E. F. besteht ein splanchnoperipheres Gleichgewicht. Eine Erweiterung der Splanchnicusgefässe führt zu einer Vermehrung der Leukozytenwerte dieser Gefässe, mit einer gleichzeitigen Kontraktion der Blutgefässe und Verminderung der Leukozytenwerte der Peripherie.

EIGENES MATERIAL.

Mein Material umfasst insgesamt 139 Versuche, von denen 30 an Meerschweinchen und 109 an Kindern ausgeführt worden sind.

Die Tierversuche wurden mit gesunden Meerschweinchen ausgeführt, in 11 Fällen wurde ausser dem peripheren auch das Herzblut untersucht.

Da es mir nicht möglich war, das genaue Alter der Tiere festzustellen, habe ich in den einzelnen Fällen ihr Gewicht angegeben.

Das Gewicht schwankte zwischen 140—580 g. Das Durchschnittsgewicht des gesamten Materials beträgt 372 g. Die Versuchstiere, bei denen sowohl das periphere als auch das Herzblut untersucht wurde, waren jünger.

Geschlechtlich habe ich die einzelnen Tiere nicht präzisiert, da nach den Literaturangaben kein geschlechtlicher Unterschied des Blutbildes vorhanden ist.

Sämtliche Patienten stammen aus der Kinderklinik der Universität zu Helsingfors.

Das Material besteht zum Teil aus Kindern, die zwecks klinischer Untersuchung eingeliefert worden waren. Ein grosser Teil der Fälle besteht aus Rekonvaleszenten, die irgendeine leichtere Krankheit durchgemacht hatten. Vor dem Versuch waren sie längere Zeit fieberfrei und frei von Infektionen und wiesen normale Temperaturen und eine normale Blutsenkungsgeschwindigkeit auf. Der Allgemeinzustand sämtlicher Kinder, an denen ich Versuche ausführte, war gut.

Insgesamt habe ich an Kindern 109 Versuche, davon 8 Kontrollversuche, ausgeführt.

In einem Teil der Fälle sind am selben Kinde mehrere Versuche ausgeführt worden, jedoch nie am selben Tage.

Auf die einzelnen Versuchsarten verteilt sich das Material wie folgt:

Einwirkung kalter Bäder auf das periphere Blutbild.
 Versuche (3 Kontrollversuche).
 Das Durchschnittsalter betrug 3 ½ Monate (Maximum 5 Mon.

18 T., Minimum 12 Tage).

2) Einwirkung kalter Fussbäder auf das periphere Blutbild. 38 Versuche.

Das Durschschnittsalter betrug c:a 3 Monate (Maximum 5 Mon. 21 T., Minimum 1 Monat).

A. Einwirkung kalter Milch auf das periphere Blutbild.
 Versuche.

Das Durchschnittsalter betrug c:a 3 Monate (Maximum 6 Mon. 17 Tage, Minimum 11 Tage).

B. Einwirkung eisgekühlten Bariumbreis auf das periphere Blutbild (mit Röntgenkontrolle.)

10 Versuche.

Das Durchschnittsalter betrug I Monat 27 Tage. (Maximum 4 Mon. 2 Tage, Minimum 5 Tage).

Bei 5 der 10 Fälle wurde eine Röntgenkontrolle mit $+37^{\circ}$ warmem Bariumbrei ausgeführt.

METHODIK DER HÄMATOLOGISCHEN UNTERSUCHUNGEN.

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Sämtliche Blutbilduntersuchungen wurden im klinischen Laboratorium der Kinderklinik der Universität zu Helsingfors ausgeführt.

Mit Ausnahme eines Teiles der Differenzierungen der Leukozyten, die die Oberschwester des klinischen Laboratoriums der Kinderklinik, Frl. RAKEL HANNUKSELA ausführte, habe ich alle Blutbilduntersuchungen selbst ausgeführt.

Die Blutentnahme erfolgte in den Tierversuchen aus der Ohrvene auf der Dorsalseite des Ohres. Der erste Blutstropfen wurde nicht benutzt. Bei den Kindern erfolgte die Blutentnahme nach Fersenstich mit der Francke'schen Nadel. Auch in diesen Fällen wurde der erste Blutstropfen nicht angewandt.

Folgende Blutbilduntersuchungen wurden ausgeführt:

- 1) Bestimmung des Hämoglobingehaltes.
- 2) Bestimmung des Erythrozytenwertes per mm³.
- 3) Bestimmung des Leukozytenwertes per mm³.
- 4) Berechnung des Färbeindexes der roten Blutkörperchen.
- 5) Differenzierung der weissen Blutkörperchen.

Die Bestimmung des Hämoglobingehaltes (Hb) nach Sahli wurde in allen Fällen mit demselben Haemometer (Helligs Modifikation) ausgeführt. Die Hb-Werte sind sowohl unkorrigiert als auch korrigiert angeführt. Der Haemometer war im Marienkrankenhaus zu Helsingfors standardisiert worden.

Die Korrektion beträgt 1.16. Die Hb-Gehalt-Bestimmungen wurden nach der üblichen Methode ausgeführt.

Die Zahl der Erythrozyten (Ery) wurde in einer Verdünnung 1: 200 gezählt. Die Zählung erfolgte in der Leitz-Zählkammer, graduiert nach Türk. In jedem Fall wurden 160 kleine Quadrate gezählt.

Die Leukozyten (Leuko) wurden in einer Verdünung 1:20 ($1^{0}/_{0}$ acid acet.) ebenfalls in der Türk'schen Kammer gezählt. Es wurden 8 grosse Quadrate gezählt.

Die Differenzierung der weissen Blutkörperchen umfasste 300 Leukozyten. Die Trockenpräparate wurden nach der üblichen MAY-GRÜNWALD-GIEMSA-Methode gefärbt.

Die Einteilung der Zellen in einzelne Zellkategorien erfolgte nach der Zähltafel von Schilling.

Die in Prozenten angegebenen Werte wurden in absolute Werte umgerechnet.

TIERVERSUCHE.

Mein Material umfasst 30 Versuche mit Meerschweinchen. Für jeden Versuch wurde ein neues Tier gebraucht.

Das Gewicht der einzelnen Tiere schwankte zwischen 140-580 g, das Durchschnittsgewicht betrug 372 g.

Geschlechtlich habe ich die Versuchstiere nicht differenziert, da nach Flaum keine geschlechtlichen Unterschiede des Blutbildes beobachtet worden sind.

Bevor ich näher auf die einzelnen Versuche eingehe, will ich in Kürze einiges über die Hämatologie des Meerschweinchens erwähnen.

Nach Flaum finden keine tageszeitlichen Schwankungen des Blutbildes statt, auch die Fütterung und das Alter scheinen keinen merklichen Einfluss auszuüben.

Die Angaben über die Erythrozytenwerte (Ery) sind sehr auseinandergehend. Gabbi gibt 5527000 Ery als Mittelwert an, nach Bender und de Witt ist der Mittelwert 6 Mill. Ery. Die meisten Forscher sind jedoch der Ansicht, dass der Mittelwert 5 Mill. Ery pro ccm aufweist.

Nach Meyer beträgt der Hämoglobingehalt (Hb) 87%, Sahli, Bender, de Witt geben 95% Hb als Durchschnittswert an.

Auch die Angaben über die Leukozytenwerte (Leuko) sind sehr variierend. Die einzelnen Autoren geben Werte zwischen 5600—15000 für Normalwerte an. Das Aussehen der einzelnen Zellkategorien der weissen Blutzellen unterscheidet sich in manchem von denen des Menschen.

Die Menge der Lymphozyten (Ly) besteht hauptsächlich aus kleinen Ly. Die Monozyten (Mo) haben selten runde, meist mehr oder weniger stark gebuchtete, durch wabige Chromatinstruktur charakterisierte Kerne.

Die Myelozyten (Myeloz.) werden nach den meisten Autoren im Blut normaler Meerschweinchen vermisst.

Für Normalwerte des Differentialblutbildes geben Bender und de Witt folgende Werte an: Neutrophile 35—60 %, Eosinophile 3—4 %, Basophile 1 %, Monozyten 5—8 %, Lymphozyten 35—55 %.

In grossen mononuclearen Zellen sieht man manchmal neben dem Kern Nebengebilde, sogenannte Kurloff-Körper. Die meisten Forscher nehmen an, dass es sich hierbei um grosse Lymphozyten handelt.

Ausführung der Versuche.

Die Meerschweinchen erwiesen sich als verhältnismässig resistent gegen Kälte. Ein längerer Aufenthalt in —2 —4°C hatte keine bedeutende Einwirkung auf ihre Rektaltemperatur. Daher beschloss ich die Temperatur der Tiere durch kalte Bäder zu senken.

Sämtliche Versuche wurden am Morgen vor der Fütterung ausgeführt. Die Rektaltemperatur wurde mit einem Spezialthermometer gemessen.

Die Durchschnittstemperatur des ganzen Materiales betrug 38,0°. (Max. 39,0°, Minim. 37,0°).

Nach der Temperaturmessung wurde das Gewicht der Versuchstiere bestimmt, wonach die Blutentnahme erfolgte. Die Blutproben wurden der Ohrvene, auf der Dorsalseite des Ohrläppehens, entnommen. Der erste Tropfen wurde nie benutzt. Sofort danach wurden die Tiere dem Kältereiz ausgesetzt. In den meisten Fällen erfolgte bei den Tieren eine starke Temperatursenkung durch kalte Bäder. Bei jedem Versuchstier wurde das Blut zur Blutbilduntersuchung nach dem Bade nur einmal entnommen, da die Blutentnahme aus der Ohrvene technisch grosse Schwierigkeiten aufwies. Die Ohrvenen waren nach zweimaliger Blutentnahme dermassen zerstört und thrombosiert, dass eine erneute Blutentnahme unmöglich war.

In allen 30 Fällen untersuchte ich die Veränderungen des peripheren Blutbildes nach der Abkühlung und in 11 Fällen auch das Herzblut. Das Herzblut erhielt ich durch Herzpunktion mit einer dünnen Kanüle.

Die Temperatur sank in allen Fällen bedeutend. Die Durchschnittstemperatur sämtlicher Fälle vor dem Kältereiz betrug 38,0°, durchschnittlich sank die Rektaltemperatur durch Kälteeinwirkung auf 27,0° (Minim. 24,6°).

Die Durchschnittstemperatur des Badewassers betrug 6,6° C (Max. + 12°, Minim. + 2°). Die Durchschnittsdauer des Bades betrug 9 Min. (Max. 15 Min., Minim. 3 Min.) In einigen Fällen, bei denen die Dauer des Bades kurz war (3–8 Min.), wurden die Tiere nach oder vor dem Bade für kürzere oder längere Zeit einer Umgebungstemperatur von $-2 + 10^{\circ}$ C ausgesetzt.

Jedenfalls konnte ich feststellen, dass schon ein 6 Min. dauerndes kaltes Bad die Körpertemperatur bis auf 25,2° senkt.

Veränderungen des peripheren Blutbildes.

Auffallend ist, dass die Ery-, Hb- und Leukozytenwerte bedeutend absinken.

Veränderungen des Hämoglobingehaltes.

Der durchschnittliche Hb-Gehalt betrug vor dem Kältereiz 106 % Sahli (Max. 125 %, Minim. 90 %).

Durch die Abkühlung sank der Hb-Gehalt im Durchschnitt auf 99 % (Max. 118 %, Minim. 80 %) also um 6,6 %. In einigen Fällen war das Absinken unbedeutend.

Der Hb-Gehalt ist 15 Min. nach dem Bade (10 Fälle) stark verändert; durchschnittlich um 8 % abgesunken.

Die Blutbilduntersuchung wurde nur in 3 Fällen 30 Min. nach dem Bade ausgeführt, daher habe ich diese Fälle mit denen, deren Blutbild 40 Min. nach dem Bade untersucht wurde, bei den prozentuellen Berechnungen vereint (insgesamt 11 Fälle). 30—40 Min. nach dem Bade war der Hb-Gehalt um 6,2 % niedriger als vor dem Kältereiz.

I Stunde nach dem Kältereiz ist der Hb-Gehalt um 6,7 % niedriger (7 Fälle). In einem Fall fand die Blutentnahme I St. 30 Min. nach dem Bade statt, auch hier war der Hb-Gehalt niedriger als zuvor.

Bei den jüngeren Tieren sank der Hb-Gehalt etwas stärker ab.

Veränderungen der Erythrozytenwerte.

Der Durchschnittswert der Ery betrug vor dem Bade 4950700. Durch den Kältereiz sanken die Ery-Werte durchschnittlich auf 4411700 Ery, also um 10,8 %.

Auffallend ist, dass die Ery-Werte am deutlichsten 15 Min. nach dem Bade abgesunken sind, nämlich um 12,3 % ihres Wertes vor dem Versuch.

In den Versuchen, bei denen die Blutwerte 30—40 Min. nach dem Bade bestimmt wurden, waren die Ery-Werte um 10,5 %

niedriger als vor dem Bade. Bei der Blutentnahme I St. nach dem Kältereiz war der Ery-Wert um 8,7 % niedriger als vorher.

Das Alter der Tiere hatte keinen Einfluss auf die Veränderungen der Ery-Werte.

Wie aus dem Obenerwähnten hervorgeht, weisen die Ery-Werte eine grösseres Abnahme als der Hb-Gehalt auf.

Veränderungen des Färbeindexes.

Der Färbeindex vergrösserte sich in 25 Fällen, verkleinerte sich in 4 Fällen und war in 1 Fall unverändert.

Veränderungen der Leukozytenwerte.

Auch die Leukozytenwerte sanken bedeutend.

Der Durchschnittswert der Leukozyten betrug vor der Kälteeinwirkung 8437 (Max. 16100, Minim. 2220) und sank durchschnittlich auf 5335 Leuko, also um 36,8 %.

Beim Vergleichen der Leuko-Wertveränderungen in den verschiedenen Zeitkategorien sieht man, dass die Leuko 15 Min. nach dem Bade um 33,9 % ihres Wertes vor dem Kältereiz abgesunken sind.

In den Fällen, bei denen das Blutbild 30—40 Min. nach dem Bade untersucht wurde, waren die Leukozytenwerte durchschnittlich um 43,3 % abgesunken.

r Stunde nach dem Bade sind die Leuko-Werte um 34,5 % niedriger als vor dem Kältereiz. Im Vergleich zu den Werten 30—40 Min. nach dem Kältereiz sind die Leuko-Werte schon bedeutend höher.

Das Alter scheint keinen Einfluss auf die Veränderungen der Leukozytenwerte zu haben.

Veränderungen des Differentialblutbildes.

Das Differentialblutbild weist nach Kälteeinwirkung keinerlei Regelmässigkeit auf. Das Alter und die Zeit der Blutentnahme üben keinen Einfluss aus. Die Eosinophilen fehlen in 2 Fällen nach der Kälteeinwirkung, in 17 Fällen ist ihre Anzahl gestiegen, jedenfalls ist ihre Menge so gering, dass ihre prozentuelle Verteilung auf das Blutbild nur ungefähr o bis höchstens 4 % ausmacht.

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Die Basophilen fehlen in 9 Fällen, in 15 Fällen sinkt ihre Anzahl und steigt in 6 Fällen. Auch ihre Gesamtmenge ist sehr gering und macht 0—2,0 % aus.

Die Lymphozytenanzahl vermehrt sich in 5 der 30 Fälle, durchschnittlich um 45,0 % und sinkt in 25 Fällen, durchschnittlich um 45,5 %. In 4 der 5 Fälle bei denen die Anzahl der Ly ansteigt konnte ich es bei der Blutuntersuchung 15 Min. nach dem Kältereiz feststellen.

Die Segmentkernigen sinken ebenfalls, zwar in 24 Fällen und steigen in 6 Fällen. Die Segmentkernigen sinken durchschnittlich um 52,4 % ihrer Wertes vor dem Versuch. In den 6 Fällen in denen die Anzahl der Sg ansteigt, steigt sie durchschnittlich um 36,1 %. Gleichzeitig können sowohl die Lymphozyten als auch die Segmentkernigen absinken.

Die Stabkernigen sind spärlich vertreten, ihre Anzahl steigt in 10 Fällen und sinkt in 20 Fällen. Ihre Veränderungen haben keinen Zusammenhang mit denen der Segmentkernigen. Beim Absinken der Anzahl der Segmentkernigen kann gleichzeitig ein Ansteigen der Anzahl der Stabkernigen und umgekehrt stattfinden.

Die Anzahl der Monozyten ist auch recht gering (0—7,5 %). In einem Fall waren keine Monozyten nachweisbar. In 16 Fällen sank die Anzahl der Monozyten durch den Kältereiz, ihre Anzahl stieg in 13 Fällen.

Veränderungen des Herzblutes.

In 11 der 30 Fälle wurden sowohl das periphere als auch das Herzblut untersucht.

Das Material umfasst Tiere, deren Durchschnittsgewicht 207 g. ist. Die Blutentnahme erfolgte in 5 Fällen 40 Min. und in 6 Fällen 1 St. nach dem Kältereiz.

Der durchschnittliche Ery-Wert des peripheren Blutes betrug 4578000 und des Herzblutes 4359000 Ery, das Herzblut enthält demnach c:a 4,8 % weniger Ery (in 2 Fällen war der Ery-Gehalt des Herzblutes höher).

Nach dem Kältereiz sanken die Ery-Werte der Peripherie durchschnittlich auf 3917000 also um 12,1 % des Wertes zuvor, und die Ery des Herzblutes auf durchschnittlich 3468000, also um 20,6 % des Wertes vor dem Kältereiz. Das Herzblut enthält demnach nach der Kälteeinwirkung 11,5 % weniger Ery als das periphere Blut.

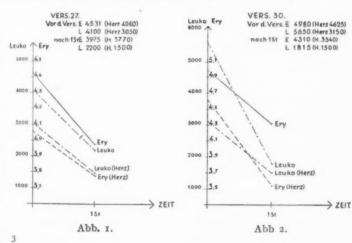
Vergleicht man die Ery-Werte vor und nach der Kälteeinwirkung, so fällt es auf, dass der Ery-Gehalt des Herzblutes bedeutend abnimmt.

Leukozyten.

Der durchschnittliche Leuko-Wert der II Fälle beträgt im peripheren Blut 6190 (Max. 9900 Minim. 2220) und im Herzblut 4388 (Max. 8200, Minim. 1500). Der Leuko-Gehalt des Herzblutes ist demnach um 29,1 % niedriger als im peripheren Blut.

Durch die Kälteeinwirkung sank der Leuko-Gehalt des peripheren Blutes durchschnittlich auf 4219, also um 32,0 % und im Herzblut auf 2948, also um 32,8 %.

Das Absinken der Leuko-Werte ist demnach beinahe gleich stark im peripheren und im Herzblut. (Abb. 1, 2.)



Der Färbeindex.

Im peripheren Blut vergrösserte sich der Färbeindex in 9 Fällen und sank in 2 Fällen.

Im Herzblut vergrösserte sich der Färbeindex in 7 und sank in 4 Fällen.

Veränderungen des Differentialblutbildes.

Die absolute Anzahl der Eosinophilen und Basophilen war äusserst spärlich, die Veränderungen ihrer Anzahl wiesen keine Regelmässigkeit auf.

Auch die Anzahl der Stabkernigen ist gering und weist keinerlei Regelmässigkeit auf. Sie können im peripheren und im Herzblut sowohl steigen als auch sinken, im gleichen Fall können die Stabkernigen im peripheren Blut nach der Kälteeinwirkung steigen und im Herzblut sinken und umgekehrt; ähnlich verhalten sich der Segmentkernigen.

Die Anzahl der Lymphozyten steigt in I Fall im peripheren Blut und sinkt in Io Fällen, im Herzblut steigt ihre Anzahl in 2 Fällen und sinkt in 9 Fällen.

Die Monozytenanzahl steigt im peripheren Blut in 7 Fällen und sinkt in 4 Fällen. Im Herzblut steigt ihre Anzahl in 4 Fällen und sinkt in 7 Fällen.

Zusammenfassung.

Auf Grund der mit Meerschweinchen ausgeführten Versuche konnte ich feststellen, dass bei Senkung der Körpertemperatur im Blutbild bedeutende Veränderungen auftreten. Die Ery-, Hb- und Leuko-Werte nehmen bedeutend ab. Auf das ganze Material verteilt sinken die Ery-Werte um 10,8 %, die Abnahme ist am deulichsten 15 Min. nach dem Kältereiz, nämlich 12,3 % des Wertes zuvor. Der Hb-Gehalt sank durchschnittlich um 6,6 %, die niedrigsten Werte stellte ich 15 Min. nach dem Kältereiz fest.

Die Anzahl der Leuko nimmt stärker ab, durchschnittlich um 36,8 %, die stärkste Abnahme konnte ich 30—40 Min. nach dem Kältereiz feststellen, 43,3 %.

In 11 Fällen wurden sowohl das periphere als auch das Herzblut untersucht. Auffallend ist, dass sowohl der Ery-, Hb- und Leuko-Gehalt des Herzblutes niedriger als im peripheren Blut ist, und dass die Ery-Werte durch die Kälteeinwirkung bedeutend stärker im Herzblut absinken, um 20,6 %, im peripheren Blut dagegen um 12,2 %. Die Leuko-Werte sinken im peripheren und Herzblut beinahe gleich stark ab, im ersteren um 32,0 % und im letzteren um 32,8 %.

Das Differentialblutbild weist keinerlei Regelmässigkeit auf. Mit Ausnahme der Veränderungen der Zahl der Ly und Sg die in den meisten Fällen nach dem Kältereiz sinkt.*

 $^{^{\}ast}$ Die Kasuistik der Versuche ist in der Universitätsbibliothek zu Helsingfors deponiert.

ÜBER DIE EINWIRKUNG KALTER VOLL-BÄDER AUF DAS PERIPHERE BLUT-BILD DES SÄUGLINGS.

Das Material umfasst insgesamt 20 Versuche von denen $_3$ Kontrollversuche mit Bädern von $+37^{\circ}$ C sind.

Sämtliche Kinder, die den kalten oder warmen Bädern ausgesetzt wurden, hatten ein gutes Allgemeinbefinden.

Den kalten Bädern wurden 5 Kinder in 17 Versuchen ausgesetzt; am selben Kinde wurden die Versuche an verschiedenen Tagen ausgeführt.

Das Alter der Kinder schwankte zwischen 12 Tagen—5 Mon. 18 Tagen. Das durchschnittliche Geburtsgewicht der Fälle betrug 3570 g (Max. 4000, Minim. 2750 g).

Sämtliche Versuche wurden frühstens 4 St. nach der letzten Nahrungsaufnahme ausgeführt.

Ausführung der Versuche.

Die Kinder wurden gewogen, ihre Rektaltemperatur wurde gemessen. Danach wurden die Kinder für 8—15 Min. einem kalten Vollbad, dessen Durchschnittstemperatur + 12,2° C (Max. + 17° C, Minim. + 9° C) betrug ausgesetzt.

In sämtlichen Fällen sank die Körpertemperatur bedeutend. Die Durchschnittstemperatur vor dem Bade betrug 36,8° (Max. 37,2°, Minim. 36,6°), sofort nach dem Bade war die Körpertemperatur durchschnittlich auf 31,2°, also um 15,2 % gesunken.

Vergleicht man die Blutbilder, so fällt es auf, dass erhebliche Veränderungen durch die Kälteeinwirkung erfolgen. Auffallend ist, dass die Ery-,Hb-Werte absinken und Leuko-Werte ansteigen. Vor dem Versuch betrug der durchschnittliche Ery-Wert 3804400 (Max. 5350000, Minim. 2460000) und 1—4 Stun-

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den nach dem Bade 3275800; der Ery-Wert war also durchschnittlich um 13,9 % abgesunken.

Der Durchschnitts Hb-Gehalt betrug vor dem Versuch 85 % (Max. 130 %, Minim. 58 %) und sank auf 81,1 %, also um 4,6 %.

Die Leuko-Werte wiesen auch grosse Veränderungen auf. Ihr Durchschnittswert betrug vor dem Versuch 7516 (Max. 12500, Minim. 4300); I—4 St. nach dem Bade betrug ihr Wert 11416, ihre Anzahl war also um 51,9 % angestiegen. In den einzelnen Fällen war ihre Anzahl sehr bedeutend angestiegen, bis max. 223 %.

Um eine deutlichere Übersicht über die Blutbildveränderungen zu erhalten, führe ich die Versuche in Gruppen geordnet an.

Wie aus der Tabelle I hervorgeht, sind die Veränderungen des Blutbildes unter fast identischen Verhältnissen recht verschieden. In 7 von 8 Fällen wurde das Blutbild I St. 30 Min. nach dem Bade untersucht.

Die Temperatur der Bäder schwankte zwischen + 10—15° C. Die Körpertemperatur sank um c:a 3,4—6,4°.

In sämtlichen Fällen sanken die Ery-und Hb-Werte. Die Leuko Werte stiegen auffallend. Die kleinen Variierungen der Temperatur scheinen keinen bedeutenden Einfluss auf die Ery-Werte zu haben, so z. B. sinkt die Körpertemp. in Versuch 4 um 3,4° und der Ery-Wert um 27,6°, dagegen sinkt die Körpertemp. in Versuch 11 um 6,3° und der Ery-Wert um 5,6 %; in Versuch 10 wiederum sinkt die Körpertemp. um 6,4° und der Ery-Wert um 14 %.

Der Hb-Gehalt nimmt durchschnittlich um 6 % ab.

Die Leuko-Werte steigen in allen ausser 2 Fällen — wie aus der Tabelle ersichtlich — bedeutend, in Fall 10 sogar um 223 %.

Im Verhältnis zu den Temperaturveränderungen kann man folgendes feststellen: in Versuch 7 sinkt die Körpertemperatur um 4,6, der Leuko-Wert steigt um 19,3, in Versuch 4 sinkt die Temp. um 3,4° und der Leuko-Wert steigt um 23,3%, dagegen sinkt die Körpertemp. in Versuch 8 um 5,6° und der Leuko-Wert steigt um 163,4%. Im Versuch 10 sinkt die Körpertemp. um 6,4° und der Leuko-Wert steigt um 223%. Möglich, dass es sich hierbei um einen Zufall handelt.

M-K , E , geb. am 11. XI. 46, Geb. Gewicht 3600 g. Dgn. Myxoedema TABELLE N:0 1

	Ge- wicht	Kältereiz	Zeit		To	T° Hb Ery	Ery	Ery Diff.		Leuko		Leuko Diff.	Diff.
12. 4. 47 4500		15 Min. + 12°C Bad Körpert° sofort danach 30,5°	Vor d. Bade nach 25' nach 1 St. 3	,00	7.4	36,7 58/68 2925 27,4 56/65 2840 31,4 36/65 2715	36.7 58/68 2925 27.4 56/65 2840 31.4 36/65 2715	—85 (2,9 %) 11750 —210 (7,2 %) 12300	(% 2.7	5650 11750 12300	++	6100 (108 %)	08 %)
15. 4. 47 4480		15 Min. + 15° C Bad	Vor d. B.	60	17.0	37,0 56/65 2895	2895			4750			
		danach 32,5°	nach 1 St. 30'		1,4	31,4 50/58 2685	2685	-210 (7.3 %)	210 (7,3 %) 10075	+	5325 (112 %)	12 %)
100	16. 4. 47 4560	15 Min. + 12°C Bad Körpert° sofort danach 32,6°	Vor d. B. nach 1 St.	m m	3,0	36,4 60/70 2945 33,0 52/61 2130	2945	-815 (27,6 %)	(% 9"	4300	+	1000	1000 (23.3 %)
	21. 4. 47 4820	7 Min. + 13°C Bad Körpert° sofort danach 33,4°	Vor d. B. nach 1 St.	30, 3	6,6	36,6 54/63 2795 32,0 50,58 2315	2795	— 480 (I7.1 %)	(% 1.7		+	1200	6200 7400 + 1200 (19,3 %)
	23. 4. 47 4820	ro Min. + 12°C Bad Körpert° sofort danach 33,7°	Vor d. B. nach 1 St.	30,	9,9	56/65	36,6 56/65 2975 31,0 54/63 2785	190 (6,4 %)	6,4 %)	4050	+	9620 (1	6620 (163,4 %)
	25. 4. 47 4820	8 Min. + 10°C Bad Körpert° sofort	Vor d. B. nach 1 St.	30, 3	1,71	37,1 58/68 2895 31,4 56/65 2725	37,1 58/68 2895 31,4 56/65 2725	(% 6'5) 0/1 —	(% 6'9	5170	+	5130	5130 (99,2 %)
	11 26.4.47 4780	ro Min. + 10°C Bad Körpert° sofort	Vor d. B. nach I St.	30, 3	6.7	36,7 30/58 2460 30,4 50/58 2323	2460	-137 (2,6 %)	137 (5.6 %) 14700 +	+	(% 221) 0056	(% 14)
	10 29.4.47 4750	Io Min. + 10°C Bad Körpert° sofort danach 31.7	Vor d. B. nach 1 St.	30, 3	17.1	37.1 52/61 2710 30.7 50/58 2330	37,1 52/61 2710 30.7 50/58 2330	- 380 (14 %)	(%)	5300		+ 11700 (223 %)	23 %)

Zu- und Abnahme der Hb., Ery- u. Leuko-Werte in % vom Werte vor dem Bade,

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Wie aus der Tabelle 2 hervorgeht, erfolgte die Blutentnahme nach dem Bade später als bei den Versuchen, die in Tabelle 1 angeführt wurden.

Die Ery-und Hb-Werte sind auch hier nach dem Bade niedriger. Die Leuko-Werte dagegen weisen nicht mehr eine so starke Zunahme auf, in Versuch 14 haben sie sogar abgenommen. Die Ery-Werte sind durchschnittlich um 7,8 % abgesunken und der Hb-Gehalt um 6,7 %.

Auch bei M. S. Tabelle 3 sinken die Ery-Werte durch die Kälteeinwirkung ab. Die Temperatursenkung ist, wie aus der Tabelle hervorgeht, recht bedeutend. In Fall 2 und 3 sinkt sie um c:a 10°. Der Ery-Wert sinkt auch etwas stärker als in den früher erwähnten Fällen. Die Leuko-Werte steigen, sind aber bei Versuch 3 4 St. nach dem Bade niedriger (um 1,9 %), obgleich sie 45 Min. nach dem Bade um 115 % höher als vor dem Versuch sind. Auch bei den beiden anderen Fällen fällt es auf, dass die Leuko-Werte in der letzten Blutentnahme, im Vergleich zu den Werten vor dem Kältereiz, recht unbedeutend erhöht sind, dagegen weisen sie eine bedeutende Zunahme 10—45 Min. nach dem Bade auf.

Vergleicht man die einzelnen in den Tabellen angeführten Versuche, so fällt es auf, dass die Ery-Werte in allen sinken, auch der Hb-Gehalt sinkt, jedoch im Verhältnis nicht gleich bedeutend wie der Ery-Wert.

Die Leuko-Werte steigen in fast allen Versuchen bedeutend.

Veränderungen des Differentialblutbildes.

Die Veränderungen des Differentialblutbildes weisen nicht eine so grosse Regelmässigkeit auf wie die Veränderungen der Ery,-Hb-und Leuko-Werte. Die Eosinophilen sind recht gering vertreten. In einigen Fällen fehlen sie vor der Kälteeinwirkung, treten aber danach auf, in anderen wiederum sinkt ihre Anzahl durch die Kälteeinwirkung.

Auf das gesamte Material verteilt ist die Anzahl der Eos durchschnittlich um 43,6 % erhöht, da ihre Anzahlveränderungen jedoch sehr schwankend sind, muss man den Prozentwert für unexakt ansehen.

TABELLE N:0 2

S. S. Geb. am 28. 3. 47. Geb. Gewicht 4000 g. Dgn. Monstrum

Leuko Diff.	289 (6,9 %) 11450 + 1400 (13,9 %)	Vor d. B. 36.7 85/98 4335 — 11400 — 11700 hach 2 St. 30' 34.6 82/92 4095 — 240 (5.5 %) 17900 + 6500 (57.2 %)	2500 8400 4100 (34.1 %)
Leuko	11450	11400	12500
Ery Diff.		240 (5.5 %)	Vor d. B. 36,9 90/104 4600 — 100 (11 %)
Ery	4175	4335	4600
T° Hb Ery	36.7 82/95 4175 34.6 78/90 2886	36.7 85/98 4335 34.6 82/92 4095	36,9 90/104 4600 34,4 82/95 4090
To	36,7	36.7	36,9
Zeit	Vor d. B. nach 2 St. 30'	Vor d. B. nach 2 St. 30'	Vor d. B. nach 2 St. 45'
Kältereiz	8. 5. 47 3480 8 Min. + 10° C Bad Körpert° sofort danach 31.4°	13 9. 5. 47 3480 15 Min. + 10° C Bad Vor d. B. Körpert° sofort nach 2 St. danach 29,1°	14 10. 5. 47 3320 12 Min. + 9°C Bad Körpert° sofort danach 27,6
Ge- wicht	3480	3480	3320
Dat.	8. 5. 47	9. 5. 47	10. 5. 47
N:0	12	13	4 T

Zu- und Abnahme der Hb-, Ery- u. Leuko-Werte in % vom Werte vor dem Bade.

TABELLE N:0 3

M. S. Geb. am 13. 4. 47. Geb. Gewicht 3800 g. Dgn. Debilitas cong.

Dat.	Ge- wicht	Kältereiz	Zeit	To	T° Hb Ery	Ery	Ery Diff.	Leuko	Lei	Leuko Diff.
*	7 3650	15 21. 5. 47 3650 12 Min. + 14; C Bad Vor d. B. Körpert° sofort nach 10' danach 27,6° nach 3 St	Vor d. B. nach 10' nach 3 St.	36,5	36,5 82/95 27,6 76/88 25,7 70/81	4395 3715 3495	4395 — 680 (15.4 %) 17650 + 10050 (132.2 %) 3495 — 900 (20.4 %) 9700 + 2100 (27.6 %)	7600 17650 9700	+ 10050	(132,2 %)
4	7 3640	2 13. 5. 47 3640 15 Min. + 12°C Bad Vor d. B. Körpert° sofort nach 30° and 30° and 2 Sl	Vor d. B. nach 30' nach 2 St.	36,7 26,5 29,4	26,5 72/83 29,4 78/90	4265 3710 4010	— 555 (13 %) — 255 (6 %)	12700 + 1 11650 +	+ 1850	12700 + 1850 (17 %) 11650 + 800 (7.4 %)
4	7 3650	3 15. 5. 47 3650 15 Min. + 10° C Bad Körpert° sofort danach 28,5°	Vor d. B. nach 45' nach 4 St.	36,9 26,4 35,1	36,9 86/100 4630 26,4 78/90 4045 35,1 83/96 4185	4630 4045 4185	36,9 86/100 4630 — 6700 — 6700 — 26,4 78/90 4045 — 585 (12,6 %) 14450 + 7750 (115,6 %) 33,1 83/96 4185 — 465 (10 %) — 125 (1,9 %)	6700	+ 7750	(115,6 %)

Zu- und Abnahme der Hb., Ery- u. Leuko-Werte in % vom Werte vor dem Bade.

Die Basophilen treten sehr spärlich auf. In mehreren Versuchen sind sie im Differentialblutbild überhaupt nicht nachweisbar. In den Versuchen, in denen sie vorkommen, kann ihre Anzahl durch der Kältereiz sowohl abnehmen als auch zunehmen, oder sie können vor dem Kältereiz fehlen und danach auftreten.

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Die Gesamtzahl der Basophilen ist jedoch sehr gering, so dass sie keinen bedeutenden Einfluss auf das gesamte Differentialblutbild ausüben.

Die Stabkernigen sind dagegen nach dem Bade regelmässig vermehrt, es erfolgt ein Anstieg um 140,9 %.

Die Anzahl der Segmentkernigen steigt in 16 von 17 Versuchen, auf das ganze Material verteilt erfolgt ein Anstieg um 50,1 %.

Die Lymphozyten-Werte weisen keine Regelmässigkeit auf. Ihre Anzahl kann sowohl steigen als auch sinken. Jedoch dominiert eine Zunahme der Anzahl. In 7 Fällen sinkt der Ly-Wert durchschn. um 19,6 % und steigt in 10 Fällen durchschn. um 92,7 % vom Wert vor dem Kältereiz.

Die Monozyten können ebenfalls sowohl zu- als auch abnehmen, jedoch überwiegt die Zunahme (12 Fälle.).

In den meisten Fällen, bei denen ihre Anzahl abnimmt, erfolgt auch gleichzeitig eine Abnahme der Ly-Werte.

Die Kontrollversuche.

Die Kontrollversuche wurden in gleicher Weise wie die Versuche mit kalten Bädern ausgeführt, mit Ausnahme, dass die T° des Badewassers + 37° C betrug.

Die Kinder wurden für 12 Minuten warmen Bädern ausgesetzt.

Die Blutentnahme erfolgte 45, 50, 60 Min. nach dem Bade. Die Körpertemperatur weist so gut wie keine Veränderung auf. Die Veränderungen der Ery-, Hb- und Leuko-Werte sind völlig unbedeutend und liegen im Bereich der Fehlergrenze.

Das Differentialblutbild dagegen weist grössere Schwankungen auf. Die Eos, Basoph., St. und Mo Werte zeigen keinerlei Regelmässigkeit, ihre Anzahl kann sowohl steigen als auch absinken. Die Anzahl der Segmentkernigen sinkt in allen 3 Versuchen. Die Ly-Werte sind in einem Versuch unverändert und steigen in den beiden anderen.

Zusammenfassung.

Aus den Versuchen geht hervor, dass die Körpertemperatur durch kalte Bäder stark absinkt und dass gleichzeitig im Blutbilde bedeutende Veränderungen auftreten.

Am deutlichsten sind die Veränderungen der Ery-, Hb- und Leuko-Werte. Die Ery-Werte sinken durchschnittlich um 13,9 % (Max. 27 %), der Hb-Gehalt sinkt nicht gleich stark, sondern durchschnittlich um 4,6 %.

Die Leuko-Werte steigen stark an, durchschnittlich um 51,9 % (Max. 223 %).

Das Differentialblutbild weist starke Schwankungen auf, die jedoch unregelmässig sind. Eine gewisse Regelmässigkeit fällt jedoch in den Veränderungen der Werte der St und Sg, erstere nehmen in sämtlichen Fällen stark zu (140,9 %), die Segmentkernigen nehmen in 16 von 17 Fällen zu, durchschn. um 50,1 %. In 7 Fällen sinkt der Ly-Wert durchschnittlich um 19,6 % und steigt in 10 Fällen durchschnittlich um 92,7 % vom Werte vor dem Kältereiz. Aus den Kontrollversuchen ist ersichtlich, dass die Hb-, Ery- und Leuko-Werte nach + 37° C Bädern so gut wie unverändert sind. Das Differentialblutbild weist dagegen grössere Schwankungen auf.*

^{*} Die Kasuistik der Versuche ist in der Universitätsbibliothek zu Helsingfors deponiert.

ÜBER DEN EINFLUSS LOKALER KÄLTE-EINWIRKUNG AUF DAS PERIPHERE BLUTBILD.

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Das Material umfasst insgesamt 38 Versuche. In einigen Fällen ist der Versuch am selben Kinde 2—3 Mal ausgeführt worden.

Das Alter der Kinder schwankte zwischen i Monat—5 Monat 21 Tagen. Im Material sind keine Frühgeburten aufgenommen worden. Der Gesundheitszustand der Kinder war gut. Sämtliche Kinder waren frei von Infektionen und hatten eine normale Körpertemperatur.

Ausführung der Versuche.

Sämtliche Versuche wurden frühestens 4 Stunden nach der letzten Nahrungsaufnahme ausgeführt. Nach Messung der Rektaltemperatur erfolgte die Entnahme der Blutproben für die Blutbilduntersuchungen. Das Blut wurde durch Fersenstich entnommen. Sofort danach wurde das eine Bein der Kinder für 15 Minuten einem kalten Bad, dessen Temperatur 5—6° C betrug, ausgesetzt. Die Kinder hatten ihre gewöhnliche Kleidung an. Der Abschnitt bis zum Knie wurde im Bade gehalten. Während dem Bade verhielten die Kinder sich ruhig.

Sofort nach dem Bade wurde die Rektaltemperatur gemessen, und die Kinder wurden mit der gleichen Menge Decken wie zuvor zugedeckt. Während dem Bade fand eine starke lokal genau abgegrenzte Rötung der Haut des im Bade befindlichen Beines statt, die ungefähr in 3—4 Minuten auftrat und 15—20 Minuten nach dem Bade anhielt, wonach ein Ablassen erfolgte.

Die Entnahme der Blutproben nach dem Bade erfolgte in verschiedenen Zeitabschnitten. Die erste Blutprobe nach dem Bade wurde in sämtlichen Fällen dem ungebadeten Bein entnommen.

Wie aus dem Material hervorgeht, sank die Körpertemperatur recht unbedeutend. In den meisten Fällen erfolgte eine vorübergehende Temperaturabnahme, die in einzelnen Fällen über 1° betrug, meist sank die Temperatur jedoch nur um einige Zehntel Grad und hatte ungefähr 1 Stunde nach dem Bade wieder den Ausgangswert erreicht.

Die geringen Körpertemperaturschwankungen sowie das Alter hatten keinen Einfluss auf die Blutbildveränderungen. Die Temperatur sank in keinem Fall unter 35,4°.

Auffallend ist, dass die lokale Kälteeinwirkung bedeutende vorübergehende Veränderungen des Blutbildes hervorruft.

In sämtlichen Fällen wurden der Ery-, Hb- und Leukozytenwert sowie das Differentialblutbild bestimmt.

Die erste Blutprobe nach dem Bade wurde in allen Fällen der Ferse des ungebadeten Beines entnommen. Danach wurden in verschiedenen Zeitabschnitten sowohl die Blutbilder des ungebadeten sowie des Blutes der der Kälte ausgesetzten Extremität untersucht. Schon bei oberflächlicher Betrachtung der Ergebnisse fällt es auf, dass die bei gleichen Zeiteinheiten nach dem Bade entnommenen Blutbilder des aus dem gebadeten und ungebadeten Fusse entnommenen Blutes nicht identisch sind, sondern oft recht erhebliche Unterschiede aufweisen.

Charakteristisch ist, dass der Ery-Wert in allen 38 Fällen nach dem Kältereiz sowohl im Blute des Kontroll- als auch des Versuchsbeines absinkt. Der Hb-Wert sinkt ebenfalls, jedoch nicht so stark wie der Ery-Wert. Dagegen weisen die Veränderungen der Leuko-Werte keine Regelmässigkeit auf, sie können sowohl sinken als auch ansteigen. In dem aus dem Versuchsbein entnommenen Blut kann der Leuko-Wert nach dem Bade höher als vor dem Versuch sein, wogegen man gleichzeitig im Blut des Kontrollbeines niedrigere Leuko-Werte als vor dem Bade feststellen kann und umgekehrt.

Veränderungen der Ery-Werte.

In den nach verschiedenen Zeiteinheiten entnommenen Blutproben verteilt sich der Ery-Wert des gesamten Materiales wie aus der Tabelle 4 hervorgeht.

TABELLE N:0 4

Veränderungen der Ery-Werte

			Kontrollbl.			Versuchsbl.
Anzahl d. Fälle	Zeit	Veränd. in %	Ery Mittel- wert nach d. Bade	Ery Mittel- wert vor d. Bade	Ery Mittel- wert nach d. Bade	Veränd. in %
38	Vor d. Versuch			3740		
3	15' nach d. Bade	+ 4,6	3852	3672		+
IO	30' nach d. Bade	6 -	3333	3663		
6	45' nach d. Bade	6 1	3628	3986		
II	I St. nach d. Bade	8'6 -	3323	3684		
6	I St. 15' nach d. Bade	6'6 -	3301	3662	3246	— II,3
15	1 St. 30' nach d. Bade	- 12	3346	3804	3262	14,1
6	2 St. nach d. Bade	8,5	3661	3990	3560	7'01 —
5	2 St. 3o' nach d. Bade	7.4	3245	3506	3123	6'0I —
21	3 St. nach d. Bade	4	3556	3705	3410	6.2 —
						in 6 Fällen unbed.
						über d. Wert vor
						dem Versuch
11	3 St. 30' nach d. Bade	+ 0.7	3052	3025	3681	- 6,2

Zu- (+) und Abnahme (--) der Ery-Werte in % vom Werte vor dem Bade.

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Wie aus der Tabelle hervorgeht sinkt der Ery-Wert nach der Kälteeinwirkung sowohl im Blut, das der der Kälte ausgesetzten Extremität als auch im Blut, das der Kontrollextremität entnommen worden ist, bedeutend.

In 3 Fällen wurde das Blut 15 Minuten nach dem Bade entnommen und war durchschnittlich um 4,6 % höher als der Wert
vor dem Bade (Versuch 1, 2, 3). 30 Minuten nach dem Bade
war der Ery-Wert schon in fast allen Fällen bedeutend abgesunken (Versuch 4, 5, 6, 7, 8, 9, 10, 11, 12, 13). Der Ery-Wert
sank durchschnittlich im Blute der Kontrollextremität um 9 %
vom Wert vor dem Bade. In einzelnen Fällen konnte ich jedoch
grössere Differenzen feststellen, so sank der Ery-Wert z. B. in
Versuch 4 um 20 %, in Versuch 8 um 16,7 %, dagegen in Versuch 5 um 4,1 % und in Versuch 12 um 8 %, im selben Fall
war der Ery-Wert des aus dem Versuchsbein entnommenen
Blutes um 13,6 % niedriger als vor dem Bade. In Versuch 9
war der Ery-Wert um 4,7 % und in Versuch 6 um 1,6 % höher
als vor dem Bade.

45 Minuten nach dem Bade war der Ery-Wert in sämtlichen Fällen abgesunken (Vers. 14, 15, 16, 17, 18, 19, 20, 21, 22), durchschnittlich um 9 %, in Versuch 18 um 1,6 %, in Versuch 14 dagegen um 19,5 %, im letzteren Fall war der Ery-Wert des der Kälte ausgesetzten Beines um 13,5 % niedriger als vor dem Bade.

I Stunde nach dem Bade beträgt die Abnahme der Ery-Werte durchschnittlich 9,8 % (Vers. 23—33).

I Stunde 15 Minuten nach dem Bade ist der Ery-Wert durchschnittlich um 9,9 % niedriger als vor dem Bade (Vers. 1, 2, 3, 5, 34, 35, 36, 37, 38), dagegen ist der Ery-Wert im Blute der der Kälte ausgesetzten Extremität um 11,3 % niedriger als vor dem Bade.

I Stunde 30 Minuten nach dem Bade ist der Ery-Wert durchschnittlich um 12 % niedriger als vor dem Versuch, auch im Blute, das der der Kälte ausgesetzten Extremität entnommen wurde, sieht man hier die niedrigsten Ery-Werte, 14,1 %. (Vers. 4,6—14, 15—21.) Der Ery-Wert kann in den Blutproben, die in denselben Zeiteinheiten nach dem Bade im selben Fall entnommen sind, im Blute der der Kälte ausgesetzten Extremi-

tät bedeutend niedriger als im Blut der ungebadeten Extremität sein und umgekehrt.

Z. B.	Vers. 16	Vor dem Bade	Erv	4055	
23. 22.	10.0. 10	nach 1 St. 30'	Kontrollb.	3435	(-15,2 %)
			Versuchsb.		(-24,4 %)
	Vers. 13	Vor dem Bade	Ery	3300	
		nach 1 St. 30'	Kontrollb.	2360	(- 28,4 %)
			Versuchsb.	3180	(- 3.7 %)
	Vers. 9	Vor dem Bade	Ery	3785	
		nach 1 St. 30'	Kontrollb.	3340	(-11,8 %)
			Versuchsb.	3305	(-12,7 %)

Zwei Stunden nach dem Bade ist der Mittel Ery-Wert im Vergleich zum Mittelwert I Stunde 30 Minuten nach dem Bade bedeutend höher, jedoch immerhin noch um 8,5 % niedriger als vor dem Bade. Im aus dem Versuchsbein entnommenen Blute ist der Wert ebenfalls im Vergleich zum Werte I Stunde 30 Minuten nach dem Bade höher, er ist jedenfalls noch um 10,7 % niedriger als vor dem Bade. (Vers. 21, 22, 27, 28, 29, 30, 31, 32, 33.)

2 Stunden 30 Minuten nach dem Bade ist der Ery-Wert im aus dem Kontrollbein entnommenen Blut um 7,4 % niedriger als vor dem Bade, dagegen ist der Ery-Wert des aus dem Versuchsbein entnommenen Blutes fast der gleiche wie 2 Stunden nach dem Bade, nämlich um 10,9 % niedriger als vor dem Bade. Insgesamt sind nur in 5 Fällen die Ery-Wert Bestimmungen ausgeführt worden, so dass man die Werte wegen der geringen Zahl der Fälle nicht für sicher ansehen kann. (Vers. 1, 2, 3, 14, 23.) Die Werte der einzelnen Versuche können recht variierend sein z. B. Versuch 14. Im aus dem Kontrollbein entnommenen Blut ist der Ery-Wert um 17,9 % niedriger als vor dem Bade, im aus dem Versuchsbein entnommenen Blut dagegen um 13,6 % niedriger. Im Versuch 1 sind die Werte wiederum wie folgt:

Kontrollbein	-12,9	%
Versuchsbein	-19,2	20

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3 Stunden nach dem Bade ist der Mittel Ery-Wert des Kontrollblutes um 4 % niedriger als vor dem Bade (Vers. 4, 6—12,

13, 15—21, 24—28, 35—38). Im Blute des Versuchsbeines ist der Ery-Wert immerhin durchschnittlich um 7,9 % niedriger als vor dem Bade, dagegen ist der Ery-Wert in 6 der 21 Fälle unbedeutend höher als vor dem Versuch.

3 Stunden 30 Minuten nach dem Bade ist der Ery-Wert des Kontrollblutbildes durchschnittlich um 0,7 % höher als vor dem Bade, dagegen ist der Ery-Wert des Blutes der gebadeten Extremität immerhin noch um 6,2 % niedriger als vor dem Bade. (Vers. 5, 21, 22, 28, 29, 30—35, 38.)

Veränderungen des Hb-Gehaltes.

Auch im Hb-Gehalt treten Veränderungen sowohl im Blutbild des Kontrollbeines als auch im Blut der direkt der Kälte ausgesetzten Extremität auf. Die Veränderungen weisen jedoch nicht eine so grosse Regelmässigkeit wie die der Ery-Werte auf. In einigen Zeiteinheiten nach dem Kältereiz kann der Hb-Gehalt z. B. im Blut der der Kälte ausgesetzt gewesenen Extremität höher als im Blute der ungebadeten Extremität sein; diese umgekehrte Differenz kann man zwar nur beim Mittelwert 2 Stunden 30 Minuten nach der Kälteeinwirkung feststellen.

Auf das gesamte Material verteilen sich die Veränderungen wie aus der Tabelle 5 hervorgeht.

Die Abnahme des Hb-Gehaltes erfolgt ersichtlich in ähnlicher Weise wie die der Ery-, die grösste Hb-Gehaltabnahme tritt jedoch 2 Stunden nach dem Bade auf.

Veränderungen des Färbeindexes.

Der Färbeindex vergrössert sich nach der Kälteeinwirkung in den meisten Fällen, eine geringe Verkleinerung des Wertes kann auftreten. 3—3 ½ Stunden nach dem Kältereiz ist der Index Wert meist wieder abgesunken, kann jedoch auch höhere oder eventuell niedrigere Werte als vor dem Bade aufweisen.

TABELLE N:0 5

Veränderungen der Hb-Werte

Amzohi		Kontrollb.	ollb.	Hb Mittel-	Versuchsb.	chsb.
d. Fälle	Zeit	Veränd. in %	Hb Mittelw.	wert vor dem Bade	Hb Mittelw.	Veränd. in %
38	Vor dem Bade			77.5		
150	15' nach d. Bade	+ 4.5	73,0	76.3		
10	30' nach d. Bade	- 5,1	70,2	74.8		
6	45' nach d. Bade	6'9 —	77,0	82,7		
11	I St. nach d. Bade	4.4	75.5	0.67		
6	1 St. 15' nach d. Bade	-5.7	69,5	73.7	67.5	- 8,0
15	r St. 3o' nach d. Bade	- 5.9	72,0	76,5	70,3	0'8-
6	2 St. nach d. Bade	- 8,1	6'94	83,8	76,0	- 9,3
25	2 St. 3o' nach d. Bade	- 2,8	69,4	71.4	20,0	6'1-
21	3 St. nach d. Bade	4.5	73.3	76,8	73,0	6.4
11	3 St. 3o' nach d. Bade	2,4	8o,1	82,1	76,3	- 7,1

Zu- und Abnahme der Hb-Werte in % vom Werte vor dem Bade.

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Veränderungen der Leuko-Werte.

Auffallend ist, dass die Leuko-Werte nach der Kälteeinwirkung keine Einheitlichkeit aufweisen. Ihre Anzahl kann sowohl absinken als auch ansteigen. Der Leuko-Wert kann in einzelnen Fällen nach der Kälteeinwirkung im Blut des Kontrollbeines niedriger als vor dem Bade sein, dagegen kann man im Blut der der Kälte ausgesetzten Extremität gleichzeitig höhere Leuko-Werte als vor dem Bade nachweisen und umgekehrt.

Auf das ganze Material verteilen sich die Veränderungen wie aus der Tabelle 6 hervorgeht.

Aus der Tabelle 6 geht hervor, wie stark variierend die Veränderungen der Leuko-Werte sind.

30 Minuten nach dem Bade dominiert die Zunahme der Leuko-Werte (Vers. 4, 5, 7, 8, 10, 13), wogegen der Wert in 4 der 10 Fälle (6, 9, 11, 12) abnimmt.

45 Minuten nach dem Bade dominiert dagegen die Abnahme der Leuko-Werte, gleichfalls 1 Stunde nach dem Bade.

I Stunde nach dem Bade steigt der Leuko-Wert im Kontrollblut in 5 der 9 Fälle durchschnittlich um 16,1 % vom Werte vor dem Bade, in 4 Fällen sinkt der Leuko-Wert um 9 %, dagegen ist der Leuko-Wert im Blute des der Kälte ausgesetzten Beines um 17,5 % in 8 der 9 Fälle angestiegen.

I Stunde 30 Minuten nach dem Bade ist der Leuko-Wert im Kontrollblut in 14 der 15 Fälle um 28,4 % niedriger als vor dem Bade, im Blut des Versuchsbeines dagegen ist der Leuko-Wert in 9 Fällen um 16,9 % niedriger als vor dem Bade, dagegen war der Leuko-Wert in 3 Fällen mit dem Wert vor dem Bade identisch. In 3 Fällen war der Leuko-Wert durchschnittlich um 5 % höher als vor dem Bade.

Die selbe Unregelmässigkeit kann man 2 Stunden 30 Minuten nach dem Bade beobachten, dagegen ist der Leuko-Wert 3 Stunden nach dem Bade im Kontrollblut in 14 der 21 Fälle durchschnittlich um 15,3 % niedriger als vor dem Bade und in 7 Fällen um 19 % höher als zuvor. Im Blute des Versuchsbeines ist der Leuko-Werte meistens höher als vor dem Bade, in 13 Fällen ist der Leuko-Wert durchschnittlich um 14,9 % höher als vor dem Bade, dagegen in 8 Fällen um 15,6 % niedriger als vor dem Bade.

TABELLE N:0 6

Veränderungen der Leuko-Werte

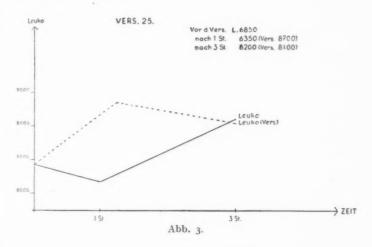
To the second	Gesamt-		Kontrollb.	ollb.			Versuchsb.	ısb.	
dem Bade	d. Fälle	Anzahl d. Fälle	Zunahme in %	Anzahl d. Fälle	Abnahme in %	Anzahl d. Fälle	Zunahme in %	Anzahl d. Fälle	Abnahme in %
15 Min.	87	64	+ 4.8	1	- 11,4				
30 Min.	IO	9	+ 25.7	4	4.61				
45 Min.	6	3	+ 41,2	9	0'81-				
ı St.	II	5	+ 14,1	9	25				
r St. 15 Min.	6	5	+ 16,1	4	6 -	œ	+ 17.5	1	- 14,4
I St. 30 Min.	15	I	+ 38,5	14	- 28,4	3	+ 5	6	6'91 —
						3	+ o		
2 St.	6	4	+ IO,2	10	- 35	5	+ 13,6	4	36,8
2 St. 30 Min.	25	3	+ 9.4	69	- 16,2	2	+ 21	3	10,4
	-	7	1,61+	14	- 15.3	13	+ 14,9	00	-15,6
3 St. 30 Min.	II	4	+ 22,0	7	31.8	10	+ 22,3	9	-33,6

Zu- und Abnahme der Leuko Werte in % vom Werte vor dem Bade.

III

3 Stunden 30 Minuten nach dem Bade ist der Leuko-Wert im Kontrollblut in 7 der 21 Fälle durchschnittlich um 31,8 % niedriger als vor dem Versuch, in 4 dagegen um 22,9 % höher als zuvor. Im Blute des Versuchsbeines kann man dagegen nicht eine so genaue Dominanz der Zunahme der Leuko-Werte feststellen. Im Kontrollblut dominiert, wie aus der Tabelle hervorgeht, die Abnahme der Leuko-Werte. In 63 Leuko-Wert Bestimmungen, kann man eine Abnahme, in 40 dagegen eine Zunahme feststellen.

Beim Beobachten der Ergebnisse der einzelnen Versuche (siehe Tabellen) fällt es auf, dass der Leuko-Wert nach der Kälteeinwirkung erst absinken, und dann wieder ansteigen kann und
umgekehrt. In diesem Zusammenhang will ich ein Beispiel
anführen. (Abb. 3.)



Veränderungen des Differentialblutbildes.

Das Hauptgewicht habe ich auf die Veränderungen des Differentialblutbildes des aus dem Kontrollbein entnommenen Blutes gelegt. Die Differentialblutbild-Werte wurden insgesamt in 37 Versuchen bestimmt. In 13 Fällen sind ausser den Werten des Kontrollblutes auch die Werte des Blutes, das aus der der Kälte ausgesetzten Extremität entnommen wurde, bestimmt worden.

Beim näheren Beobachten der Zellwerte der einzelnen Kategorien kann man in gewisser Hinsicht eine Regelmässigkeit in den Veränderungen der Anzahl der Zellen einzelner Zellkategorien nach dem Kältereiz feststellen. Beim grössten Teil der Fälle nahm die Anzahl der Lymphozyten ab und die Zahl der Segmentkernigen zu. Auch die Zahl der Monozyten vermehrte sich in den meisten Fällen, ihre absolute Zahl ist jedoch gering.

Die Eosinophilen waren verhältnismässig spärlich vorhanden. Die Basophilen fehlten im Blutbild des grössten Teiles der Versuche, ihre absolute Zahl war jedoch dermassen gering, dass die kleinen Schwankungen ihrer Anzahl vollkommen bedeutungslos sind.

Die juvenilen Neutrophilen sind äusserst selten nachweisbar. Zur näheren Darstellung der Veränderungen der Ly-Werte will ich sie in der folgenden Tabelle anführen.

TABELLE N:0 7

Veränderungen der Ly-Werte

Zeit nach dem Bade	Gesamtz. der Fälle	Anzahl der Fälle	Zunahme in %	Anzahl der Fälle	Abnahme in %
15 Min.	3	2	+ 11,3	1	— 10,0
30 Min.	. 10	5	+ 23,6	5	- 23.0
45 Min.	8	. 2	+ 38	6	24
ı St.	10	2	+ 6,3	8	- 25,7
1 St. 15 Min.	9	3	+ 23.7	6	- 14,2
1 St. 30 Min.	15	1	+ 27,6	14	- 30,0
2 St.	9	2	+ 10	7	- 19,1
2 St. 30 Min.	4	I	+ 28,8	3	- 19
3 St.	21	4	+ 17.4	17	- 20,6
3 St. 30 Min.	11	3	+ 40,8	8	- 25,1

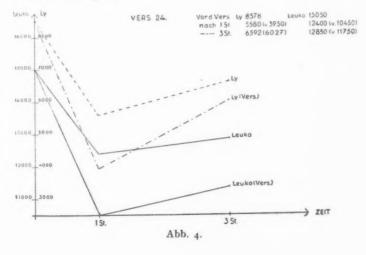
Zu- und Abnahme der Ly-Werte in % vom Werte vor dem Bade.

Wie aus der Tabelle hervorgeht, war der Ly-Wert ab 45 Minuten nach dem Bade meistens niedriger als vor dem Kältereiz. I Stunde 30 Minuten nach dem Bade ist der Ly-Wert in 14 der 15 Fälle um 39,9 % niedriger als vor dem Bade. Obgleich niedrigere Ly-Werte als vor dem Bade 3 Stunden 30 Minuten nach dem Bade dominieren, sind sie nicht mehr so ausgeprägt, wie in den Blutbildern der früheren Zeiteinheiten nach dem Bade (in 8 von 11 Fällen um 25,1 % niedriger).

In 13 Fällen wurden auch die Differentialblutbild Werte des Blutes, das der direkt der Kälte ausgesetzten Extremität entnommen worden war, bestimmt. Erfolgt ein Sinken der Ly-Werte im Blute des Kontrollbeines, so sinkt auch der Ly-Wert im Blut des gebadeten Beines. Die Ly-Werte können im aus der gebadeten Extremität entnommenen Blut stärker als in dem Kontrollbein entnommenen Blut absinken und umgekehrt. In einigen Versuchen war der Ly-Wert im Blut des Kontrollbeines nach der Kälteeinwirkung höher als zuvor, im Blute des Versuchsbeines dagegen niedriger als vor dem Kältereiz.

Zur näheren Veranschaulichung der Veränderungen will ich 2 Beispiele anführen: (Abb. 4 u. 5.)

Wie schon erwähnt erfolgt meistens ein Ansteigen der Anzahl der Segmentkernigen nach dem Kältereiz. Die einzelnen Veränderungen der Zellanzahl verteilen sich wie aus der Tabelle 8 hervorgeht.



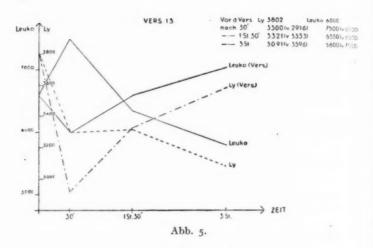


TABELLE N:0 8

Veränderungen der Anzahl der Sg

Zeit nach d. Bade	Gesamtz. d. Fälle	Anzahl d. Fälle	Zunahme in %	Anzahl d. Fälle	Abnahme in %
15 Min	3	2	+ 17,1	ī	- 13.5
30 Min	10	8	+ 31,1	2	8,1
45 Min	8	4	+ 35.4	4	- 12,4
ı St	10	9	+ 41,2	1	-13,9
1 St. 15 Min	9	5	+ 46,9	4	15
1 St. 30 Min	15	10	+ 40,0	5	- 16,6
2 St	9	5	+ 60,8	4	- 18,9
2 St. 30 Min	4	3	+ 19,2	1	- 13,6
3 St	21	14	+ 29.4	7	- 12,3
3 St. 30 Min	11	7	+ 38.7	4	- 22,8

Zu- und Abnahme in % vom Werte vor dem Fussbade.

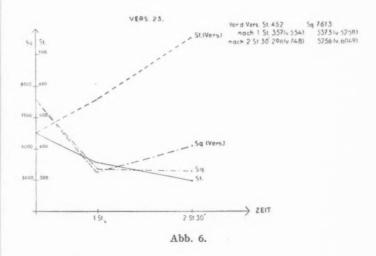
Aus der obenangeführten Tabelle geht hervor, dass die Anzahl der Segmentkernigen sich nach dem Kältereiz erheblich ändert. Vergleicht man die Werte mit denen der Lymphozyten so fällt es auf, dass in den Veränderungen der Anzahl der Segmentkernigen grössere Schwankungen auftreten.

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Vergleicht man die Werte der Segmentkernigen des Kontrollblutbildes mit den Werten der Segmentkernigen des aus dem Versuchsbein entnommenen Blutes, so sieht man eine ähnliche Unregelmässigkeit wie bei den Werten der Lymphozyten. Die Werte der Segmentkernigen können im selben Versuch in der selben Zeiteinheit im Blute des Versuchsbeines sowohl stärker als auch schwächer absinken oder ansteigen als im aus dem Kontrollbein entnommenen Blute.

Die Veränderungen der Werte der Stabkernigen sowohl im Blute des Kontrollbeines, als auch im Blute der der Kälte ausgesetzten Extremität, weisen keinen Zusammenhang auf. Beim Ansteigen der Anzahl der Stabkernigen nach dem Kältereiz im Blute des Kontrollbeines, kann gleichzeitig ein Sinken der Anzahl der Segmentkernigen erfolgen und umgekehrt.

Ein Beispiel: (Abb. 6.)



Die Veränderungen der Zahl der Mo, Eos und Bas wiesen keine Regelmässigkeit auf, ihre absolute Zahl war gering.

Das Material umfasst insgesamt 38 Versuche, die an Kindern im Alter von 1 Monat—5 Monaten 21 Tagen ausgeführt wurden. Ein Bein der Kinder wurde für 15 Minuten einem Bade von 5—6° C ausgesetzt.

Die Rektaltemperatur sank durch den lokalen Kältereiz verhältnismässig unbedeutend, jedenfalls übten die geringen Temperaturdifferenzen der Körpertemperatur keinen Einfluss auf das Blutbild aus.

In den Untersuchungen konnte ich feststellen, dass eine erhebliche vorübergehende Veränderung des Blutbildes stattfand.

Die Ery-Werte sanken in 100 % der Fälle, mit Ausnahme, dass sie 15 Minuten nach dem Kältereiz höher als zuvor sein konnlen. Im Kontrollblutbild hatten die Ery meistens 3—3 ½ Stunden nach dem Kältereiz ihren Ausgangswert wieder erreicht. Die niedrigsten Ery-Werte konnte ich 1½ Stunden nach dem Bade feststellen. Im Blut der der Kälte ausgesetzten Extremität war der Ery-Wert 3—3½ Stunden nach dem Bade höher als 1½ Stunden nach dem Bade, jedoch immerhin noch bedeutend niedriger als vor dem Kältereiz.

Auch der Hb-Gehalt sank nach dem Kältereiz, jedoch nicht so bedeutend wie der Ery-Wert.

Die Leuko-Wert Veränderungen wiesen keine Regelmässigkeit auf, mit Ausnahme, dass ihre Anzahl I Stunde 30 Minuten nach dem Kältereiz in 14 der 15 Fälle im Kontrollblutbild um — 35 % niedriger als vor dem Bade war, der entsprechende Wert betrug im Blute der der Kälte ausgesetzten Extremität — 36,8 %.

3-3¹/₂ Stunden nach dem Kältereiz dominierten in Kontrollblutbild niedrigere Leuko-Werte als vor dem Bade, dagegen waren die Leuko im Blute der der Kälte ausgesetzten Extremität in 13 der 21 Versuche um 14,9 % höher als vor dem Kältereiz.

Das Differentialblutbild wies sehr variierende Veränderungen auf. Die Anzahl der Zellen der einzelnen Zellkategorien konnte sowohl ansteigen als auch absinken. Im selben Versuche konnte z. B. nach gleich langer Zeit nach dem Kältereiz die Anzahl der Segmentkernigen im Kontrollblutbild höher als vor dem Kältereiz, im Blut der der Kälte ausgesetzten Extremität dagegen niedriger als vor dem Bade sein.

Jedoch konnte ich in den meisten Fällen eine Abnahme der Lymphozyten und eine Zunahme der Segmentkernigen nach dem Kältereiz im Differentialblutbild feststellen.

Die absolute Anzahl der Monozyten war verhältnismässig gering, in den meisten Fällen stieg ihre Anzahl nach dem Kältereiz, ähnlich war die Veränderung der Anzahl der Eosinophilen.

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TABELLE

Ober die Einwirkung halter

N:o	Name	D	atum	Alter	Zeit	T°	Hb	Ery per mn
1	M. R-O.	2	12. 47	ı Mon.	Vor d. Vers.	36,6	67/78	4245
•		-	4/		nach 15'	35.9	77/89	+530
					nach i St. 15'	36,8	61/71	3485
				1	gebad. Fuss	30,0	60/70	3275
					nach 2 St. 30'	36,8	62/72	3705
					gebad. Fuss	-	61/71	3430
2	M. R-O.	3.	12. 47	ı Mon.	Vor d. Vers.	37,0	65/75	3605
					nach 15'	36,9	62/72	3540
					nach 1 St. 15'	36,9	59/69	3270
					gebad. Fuss	-	56/65	2955
					nach 2 St. 30'	37.0	59/69	3385
					gebad. Fuss	-	61/71	3415
3	K. M.	3.	12. 47	3 ½ Mon.	Vor d. Vers.	37.3	57/66	3165
					nach 15'	37,1	58/68	3480
					nach 1 St. 15'	36,8	55/64	3050
					gebad. Fuss	-	51/60	2895
					nach 2 St. 30'	37.2	58/68	3280
					gebad. Fuss	-	58/68	3315
4	K. M.	5.	12. 47	3 Mon. 16 T.	Vor d. Vers.	37.0	58/68	3690
					nach 30'	36,1	51/60	2935
					nach 1 St. 30'	36,8	53/62	3070
1					gebad. Fuss		53/62	3050
					nach 3 St.	37,0	55/64	3320
					gebad. Fuss	_	55/64	3155
5	K. T.	19.	1. 48	3 Mon.	Vor d. Vers.	36,7	68/79	3870
					nach 30'	35.1	63/73	3710
					nach 1 St. 15'	35.5	64/74	3430
					gebad. Fuss		62/72	3170
i					nach 3 St. 30'	36,4	64/74	3695
					gebad. Fuss		64/74	3030
6	M. A.	20.	1. 48	2 Mon.	Vor d. Vers.	36,7	85/98	4855
					nach 30'	35.3	78/90	4935
					nach 1 St. 30'	36,2	76/88	4120
					gebad. Fuss	-	71/82	4145
					nach 3 St.	36,6	72/83	4260
					gebad. Fuss	-	70/81	3990
7	T. S.	21.	1. 48	3 Mon.	Vor d. Vers.	37,0	57/66	3065
					nach 30'	35.4	51/60	3050
					nach 1 St. 30'	36,4	51/60	2090
					gebad. Fuss	_	50/58	2450
					nach 3 St.	36,6	54/63	3080
					gebad. Fuss		54/63	2950

N:0 9 Fussbäder auf das Blutbild

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Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
0,93	11500	345	0	1 0	0	150	2955	8015	3.5
0,99	13350	360	0	0	0	307	3605	8944	134
1,04	11000	253	0	0	0	297	3190	7073	18
1,06	12000	240	0	0	0	276	3324	8004	150
0,97	11600	232	0	0	0	313	3283	7656	110
1,01	11150	190	0	0	0	256	3011	7548	145
1,04	9000	297	0	0	0	90	2430	6120	6
1,03	10000	350	0	0	0	50	2700	6800	100
1,05	7450	75	0	0	0	52	2384	4864	75
1,08	7700	116	39	0	0	39	1348	6004	15.
1,01	10500	137	137	0	0	137	2100	7600	399
1,04	11300	113	113	0	0	170	4927	5830	147
1,03	11350	511	34	0	0	568	1930	8012	295
0,97	10050	261	30	0	30	402	1769	7156	40.
1,05	12600	290	38	0	76	454	1462	9864	416
1,00	12800	333	0	0	38	1024	1702	9498	20
1,03	10300	515	0	0	31	855	2400	6231	268
1,03	9350	337	0	0	0	468	1805	6497	24.
0,92	7650	122	23	0	46	536	964	5737	230
1,03	10650	170	32	0	107	809	1693	7349	490
1,00	5400	178	0	0	0	324	978	3780	140
1,00	6750	115	0	0	20	520	965	5015	11
0,98	11200	370	0	0	78	706	2050	7840	146
1,00	8250	165	25	0	0	388	1495	5882	305
10,1	6420	84	0	0	0	64	1688	4391	193
0,99	8070	105	0	0	0	137	1832	5754	242
1,09	7500	23	0	0	0	0	1134	6173	173
1,14	6600		-	_	Allements.	-			-
1,01	5450	71	0	0	0	93	1183	3923	180
1,03	6550	-	-	-	-	-	_		Tribune.
1,00	6200	62	0	0	.0	81	1550	4172	335
0,92	5450	147	0	0	0	71	1526	3434	273
1,07	4700	61	0	0	0	80	1283	3008	268
00,1	5050	9-		_			_		
0,99	4850	82	15	0	0	82	1019	3526	100
1,01	4900		_	_	-		-		
1,06	7550	204	0	0	0	0	3549	3495	302
0,97	10200	275	0	0	0	102	4692	4417	714
1,00	9400	216	28	0	0	254	4982	3206	714
1,16	9300		-	-	-	-			-
1,02	7350	96	0	0	0	22	3556	3455	221
1,05	10300		-			_	-	-	-

N:o	Name	Datum	Alter	Zeit	T°	Hb	Ery per mm
	75. 4		a Man a T	Vor d. Vers.	36,6	78/90	4285
8	M. A.	2. 2. 48	2 Mon. 7. T.			72/83	1
İ				nach 30'	35,6		3570
1				nach 1 St. 30'	36,2	65/75	3535
-				gebad. Fuss		63/73	2920
				nach 3 St.	36,3	72/83	3705
1				gebad. Fuss	_	69/80	3445
9	M. A.	23. 1. 48	2. Mon.	Vor d. Vers.	36,9	73/85	3785
				nach 30'	35,6	72/83	3950
				nach 1 St. 30'	36,1	70/81	3340
				gebad. Fuss	_	70/81	3305
1				nach 3 St.	36,6	71/82	2630
				gebad. Fuss	_	71/82	3570
	Н. М.	24 2 49	2 Mon. 10 T.	Vor d. Vers.	36,6	60/70	.3380
10	ri. m.	24. 1. 48	2 41011. 10 1.	nach 30'	35,9	63/73	2895
				nach i St. 30'	36,1	60/70	2995
				gebad. Fuss	30,1	60/70	2020
i				nach 3 St.	36,5	60/70	3240
1					30,3	58/68	1
				gebad. Fuss	_	30/00	3080
11	P. K.	10. 12. 47	ı Mon.	Vor d. Vers.	36,8	51/60	2810
				nach 30'	36,3	50/58	2400
				nach 1 St. 30'	36,8	50/58	2430
				gebad. Fuss	_	50/58	2485
		i		nach 3 St.	36,8	52/61	2985
				gebad. Fuss	_	52/61	2785
12	M. O.	10 10 47	1 Mon. 12 T.	Vor d. Vers.	36,7	58/68	3585
12	M. O.	12. 14. 4/	1 34011. 12 1.	nach 30'	36,4	56/65	3298
				gebad. Fuss	30,4	56/65	3095
				nach 1 St. 30'	36,7	58/68	3475
				gebad. Fuss	30,7	56/65	3215
			. Man . 317	Vor d. Vers.	36,8	22/64	3300
13	E. A.	14. 12. 47	5 Mon. 3 W.	nach 30'		55/64	2530
				gebad. Fuss	36,7	52/61	2950
			1		-66		0.00
				nach 1 St. 30'	36,8	51/60	2360
				gebad. Fuss	_	55/64	3180
				nach 3 St.	36,8	56/65	3315
				gebad. Fuss	-	58/68	3530
14	P. R.	8. 1. 48	3 Mon.	Vor d. Vers.	36,8	64/74	365
-4	A . At.	0. 1. 40	3 44044.	nach 45'	36,6	60/70	2930
				gebad. Fuss	3-,5	60/70	3160
				nach 2 St. 30'	36,8	58/68	3000
				gebad. Fuss	30,0	57/66	1
				genau. russ		3/100	1 3.3

Fussbäder auf das Blutbild

Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
1.05	4380	31	0	0	0	74	626	3342	307
	6500	176	0	0	0	65	1235	4679	345
1,15	3550	96	0	0	0	46	1276	1988	142
1,25	3900		_	_	-	_			
1,12	4800	96	0	0	0	14	1138	3278	274
1,18	5750	_	_	- 1		_	_	-	-
1,12	7800	156	0	0	0	133	1092	6263	156
1,04	5600	56	0	0	0	112	1529	3803	95
1,20	5350	161	0	0	0	54	1246	3691	198
1,20	6250	_		_	_	_			-
1,12	5600	112	0	0	0	39	1439	3880	129
1,14	6750	_	-	-	_	-	-	-	Berrouge.
1,03	7950	24	0	0	0	80	2202	5406	56
1,25	8075	0	0	0	0	81	2203	5467	162
1,17	7100	21	0	0	0	234	2677	3742	263
1,21	8200	_		-	-	week	-	-	-
1,12	6200	0	0	0	0	124	1922	3720	372
1,10	11450	-	-	- 1	-	_		-	_
1,07	9550	478	0	0	29	353	1308	7162	220
1,16	8650	433	26	0	29	718	1585	5796	87
1,21	5900	454	0	Erythro- blast 29	20	549	1089	3696	136
1,16	9550	793	29	0	32	411	1624	6465	220
1,02	9050	661	27	0	31	570	1448	6154	181
1,05	8700	748	0	0	29	896	1435	5594	26
0,94	8450	304	0	0	0	448	1369	6109	220
0,98	6700	268	0	0	0	556	1139	4576	154
1,05	3950	316	0	0	0	316	644	2568	103
0,97	5500	347	0	0	O	292	677	4158	17
1,02	8750	438	0	0	26	376	1111	6361	403
0,97	6600	218	0	_	20	812	1472	3802	238
1,16	7500	495	23		45	1073	2145	3300	398
1,02	6000	558	0	Frythro blast 20	96	1020	1238	2916	180
1,21	6350	191	19		19	1207	1499	3321	83
1,00	6600	396	0	Erythro- blast 88	40	1360	1390	3333	152
0,98	5800	151	0	17	35	1102	1311	3091	93
0,97	7050	212	0	71	42	1431	1622	3596	212
1,00	4220		-	-	*****		-	-	-
1,21	6750	_	-				-	-	_
1,09	8900	-	_	-	-		-		_
1,13	4950	-	- Commercial Commercia	-		Minno	-	Space.	_

N:o	Name	Datum	Alter	Zeit	T°	Нь	Ery per mn
	K. K.	20. 1. 48	2 Mon.	Vor d. Vers.	36,8	73/85	
15	K. K.	20. 1. 40	2 Mon.				4135
				nach 45'	36,3	69/80	3595
				nach i St. 30'	36,9	65/75	3585
1				gebad. Fuss	-50	66/77	3535
				nach 3 St.	36,8	68/79	4025
				gebad. Fuss	_	65/75	3725
16	M. A.	27. 1. 48	2 Mon.	Vor d. Vers.	36,7	73/85	4055
				nach 45'	36,3	60/70	3400
- 1				nach 1 St. 30'	36,5	65/75	3435
				gebad. Fuss	_	66/77	3165
1				nach 3 St.	36,7	71/82	3905
				gebad. Fuss	-	69/80	3845
17	K. K.	28. 1. 48	2 Mon. 7 T.	Vor d. Vers.	36,8	70/81	3895
				nach 45'	36,1	62/72	3595
1				nach i St. 30'	36,6	67/78	3945
				gebad. Fuss	3-,0	66/77	3005
				nach 3 St.	36,8	68/79	3945
1				gebad. Fuss		68/79	3930
18		28. 1. 48	3 Mon. 11 T.	Vor d. Vers.	200	71/82	4065
10	J. J.	28. 1. 48	3 Mon. 11 1.		37.2		
1				nach 45'	37.1	69/80	4000
-				nach 1 St. 30'	37,2	64/74	3975
- 1				gebad. Frss		65/75	3933
				nach 3 St.	37,2	70/81	3910
- 1				gebad. Fuss	_	70/81	3930
19	K. K.	29. 1. 48	2 Mon. 8 T.	Vor d. Vers.	36,7	72/83	4075
				nach 45'	36,1	70/81	3835
1				nach 1 St. 30'	36,7	65/75	3630
				gebad. Fuss		66/77	3665
				nach 3 St.	36,7	70/81	4080
				gebad. Fuss	_	68/79	3790
20	K. K.	31. 1. 48	2 Mon. 10 T.	Vor d. Vers.	37,0	72/83	4080
				nach 45'	36,0	70/81	3885
-				nach i St. 30'	36,7	70/81	3605
1				gebad. Fuss	3-11	69/80	3270
				nach 3 St.	37,0	70/81	3895
				gebad. Fuss	37,0	70/81	382
	N. P.	6 0 .0	a Mon as T	Vor d. Vers.	27.1	70/81	3890
21	Av. P.	0. 2. 48	2 Mon. 24 T.		37,1	70/81	
				nach 45'	36,4		3785
				nach 2 St.	36,8	66/77	3590
				gebad. Fuss		65/75	3405
1				nach 3 St. 30' gebad. Fuss	37,0	70/81 69/80	3965
22	J. J.	6. 2. 48	2 Mon. 20 T.	Vor d. Vers.	37,2	72/83	4025
				nach 45'	36,4	66/77	3505
				nach 2 St.	36,9	68/79	3565
1				nach 3 St. 30'	37,1	70/81	4040
				gebad. Fuss		72/83	3920

Fussbäder auf das Blutbild

Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
1.04	8770	202	0	0	0	61	1956	6376	175
1,11	6900	138	0	0	0	69	1650	4968	II
1,04	6650	47	0	0	0	47	1862	4494	200
1,10	7400	-77	_	_	_			7777	
0,99	6500	III	0	0	0	85	2125	4094	8
1,01	8850	-		-	_	-	-	-	_
1,04	5300	143	0	0	0	53	1553	3445	100
1,00	4425	102	0	0	0	102	1960	2127	8
1,10	5250	173	0	0	0	121	1696	3150	IO
1,20	4950	_		-		_	-	-	-
1,05	5120	87	0	0	0	51	1295	3677	
1,05	4550			-	-	_	-	-	_
1,04	10450	178	0	0	0	105	2090	7659	41
1,00	9225	120	0	0	0	65	2306	6706	2
1,08	10400	31	0	0	0	73	3567	6416	. 31:
1,04	9200	-	-	-	-	-	-	-	-
1,00	10000	100	0	0	0	70	2400	7300	130
1,00	10950	-	-	-		-	-	-	-
1,00	5750	75	0	0	0	155	2030	3392	9
1,00	5450	38	0	0	0	16	2507	2616	27.
0,93	9350	94	0	0	0	122	4423	4329	37
0,96	9475		-	-		_	-		
1,04	7050	0	0	0	0	71	3363	3122	49
1,04	8000		-	-		_	_		_
1,01	11500	81	0	0	0	35	2151	8968	26
1,07	7800	0	0	0	0	0	1872	5794	13
1,04	6575	66	0	0	0	66	2038	4274	13
1,04	8450	- 1	_	- 1			_	-	
0,99	8400	59	0	0	0	109	2100	5796	330
1,04	8600		_	-	-	_		-	
1,01	10000	130	0	0	0	70	2000	7500	300
1,04	15750	205	0	0	0	110	3623	11292	520
1,13	9900	0	0	0	0	30	2277	7326	26
1,19	10000	-	_	-		-	_	-	_
1,04	10650	75	0	0	0	0	2800	7349	42
1,04	11900	-	_	-	-	-	_	-	_
1,04	8375	84	0	0	0	59	2764	5275	19
1,07	9350	65	0	0	0	94	2525	6386	25
1,07	7950	80	28	0	0	80	2226	5349	215
1.07	9950	-	-	_	-	0	_	-	-
1,01	9450	0	_ 0	0	_ 0	28	3119	6303	95
1,04	10000	20	0	0	0	80	7.000	8000	0.00
1,04		30 26				70	1400	8230	270
	8550		0	0	0	26	1197	6951	342
1,10	9300	121	0	0	0	71	2576 3176	6699	203
I,OI									

Ober die Einwirkung kalter

I, I, I, I,

N:o	Name	Date	am	Alter	Zeit	T°	Hb	Ery per mm
	D 75			22 T	Vor d. Vers.	36,8	58/68	2850
23	P. K.	5. 12	. 47	23 T.	nach i St.	36,6	51/60	2375
					gebad. Fuss	30,0	50/58	2185
					nach 2 St. 30'	36,8	60/70	
						0		2855
					gebad. Fuss	-	57/66	2330
24	н. к.	13. 12	. 47	3 Mon.	Vor d. Vers.	37,1	55/64	3095
					nach 1 St.	36,4	51/60	2210
					gebad. Fuss		51/60	2720
					nach 3 St.	37,1	51/60	2780
					gebad. Fuss	-	53/62	2430
25	T. S.	9. 1	48	2 Mon. 14 T.	Vor d. Vers.	37,0	69/80	3250
25	A . 53.	9. 4	. 40	2 240m. 14 2.	nach i St.	36,7	67/78	2880
					gebad. Fuss	3-11	60/70	2525
					nach 3 St.	_	62/72	2900
					gebad. Fuss	_	62/72	2870
					geoud. Tuss		02//2	10,0
26	J. A.	10. 1	. 48	2 Mon. 24 T.	Vor d. Vers.	36,8	64/74	3370
					nach I St.	35.4	62/72	3080
					gebad. Fuss	-	51/60	2750
					nach 3 St.	36,8	60/70	3370
					gebad. Fuss	-	62/72	3155
25	J. J.	2. 2	48	3 Mon. 16 T.	Vor d. Vers.	37,0	72/83	4250
27	3.3.		. 40	3 22011. 10 1.	nach i St.	36,2	70/81	3795
				+	nach 2 St.	37,0	65/75	3900
					gebad. Fuss	3//-	65/75	3800
					nach 3 St.	37,0	70/81	4210
					gebad. Fuss	-	70/81	4145
					** 1 **		66 lmm	0000
28	N. P.	13. 2	. 48	2 Mon.	Vor d. Vers.	37,0	66/77	3970
					nach 1 St.	37,0	58/68	3325
					nach 2 St.	37,0	55/64	3320
	1				gebad. Fuss	_	58/68	3225
					nach 3 St. 30'	37,0	58/68	3705
					gebad. Fuss	_	57/66	3605
29	F. V.	12. 2	. 48	2 Mon.	Vor d. Vers.	36,9	60/70	3300
					nach 1 St.	36,5	57/66	3025
					nach 2 St.	36,9	51/60	3050
					gebad. Fuss	_	51/60	3045
					nach 3 St. 30'	36,9	56/65	3120
				-	gebad. Fuss	_	56/65	3135
20	V. H-K.	11 0	48	ı Mon.	Vor d. Vers.	37,0	105/122	4935
30	v. II-K.	11. 2	. 40	i sion.	nach i St.	37,0	97/113	4885
					nach 2 St.	37,0	97/113	4710
					gebad. Fuss	37,0	95/110	4820
					nach 3 St. 30'	37,0	104/121	4870
					gebad. Fuss	37,0	102/118	
					genau. russ	-	102/110	4/00

Fussbäder auf das Blutbild

Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
1,13	10500	1050	0	0	32	452	1113	7613	243
	7600	327	0	0	23	357	1320	5373	198
1,27	8400	840	25	0	50	554	1332	5258	36
1,35	8000	904	0	0	0	296	1464	5256	8
1,42	9350	776	0	0	0	748	1655	6049	12
1.03	15050	1204	0	0		1806	3010	8578	45
1,50	12400	1054	0	0	_	2108	3348	5580	31
1.11	10450	732	0	0		2121	3616	3950	3
1.00	12850	861	0	0	. 78	1799	3302	6592	21
1,29	11750	740	0	0	35	1528	3032	6027	38
1,23	6850	308	137	0	0	993	1439	3528	44
1,36	6350	254	32	0	0	730	1651	3238	44
1,40	8700	479	0	0	44	1523	2654	3782	21
1,24	8200	328	25	0	0	1148	2025	4157	51
1,23	8100	243	41	0	0	1134	1661	4496	52
1,00	9220	304	0	0	28	1134	2462	5135	15
1,16	10750	355	108	0	75	1860	3257	4450	64
1,07	9050	299	27	0	0	1760	2652	4198	15
1,03	10100	273	0	0	0	1283	2353	5282	90
1,13	8520	426	0	0	0	1278	2471	4260	8
0,94	9950	129	0	0	0		2259	7263	20
1.07	8900	62	0	0	0		2786	5847	17
0,96	12800	90	0	0	0	27	3930	8447	33
0,99	10650	0			-	-	-	-	_
0,96	8400	59	0	0	0	25	3377	4788	22
0,99	9500		-	-	-	-	-		-
0,96	11570	150	0	0		35	3668	7370	34
1,03	7700	77	0	0	54	23	3157	4258	13
0.97	8400	84	0	0	-	59	3024	5065	16
1,05	5900	_	-		_		_	_	_
0,92	9425	94	0	0		123	2667	6475	6
0,92	10400				_	_		_	
1,06	12500	338	0	0	0	38	1711	10000	41
1,10	6575		-		_	-	_	-	_
1,00	8400	84	0	0	0	25	1377	6829	8
1,00	12350	-	-	_	-	-	_	_	_
1,02	12100	121	0	0	0	0	1767	9813	39
1,02	11400			-	-	-	_	-	
1,36	8400	109	25	0	0	0	3452	4788	1 2
1,16	8800	26	0	0	0	26	4928	3282	53
1,20	9300	28	0	0	0	28	5304	3813	13
1,14	10300	manual.	Marries.		-	-	-	- Calendaria	-
1,24	8100	57	. 0	0	0	57	4860	3126	

Ober die Einwirkung kalter

N:o	Name	D	atum	Alter	Zeit	T°	Hb	Ery per mm
21	V H K.	18.	2 48	1 Mon. 7 T.	Vor d. Vers.	37,0	82/95	1280
3.	V. A.	Ame	4. 4	I Matoria	nach i St.	36,6	82/95	1350
	1		1	1	nach 2 St.		82/95	+305
			7	1	gebad. Fuss	37,0	80/93	4200
	1		1	1			1 - 1	4150
			7	1	nach 3 St. 30' gebad. Fuss	37,0	82/95	4340
			1	1	gebad. russ	-	82/95	4320
32	F. V.	16.	2. 48	2 Mon. 4 T.	Vor d. Vers.	37.2	57/66	3500
				1	nach 1 St.	37,0	56/65	3545
			,	()	nach 2 St.	37.2	52/61	3165
	1		1	1	gebad. Fuss		50/58	2895
			,	1	nach 3 St. 30'	37.2	58/68	3850
			1		gebad. Fuss	_	51/60	2970
33	F. V.	20.	9 48	2 Mon. 8 T.	Vor d. Vers.	27.0	60/70	3560
33	F. V.	20.	2. 40	2 Mon. o	nach i St.	37,0	1	3500
,				1		36,8	56/65	3005
,			1	1	nach 2 St.	37,0	58/68	3150
,	1		,	()	gebad. Fuss	25.0	59/69	3085
,			1	1	nach 3 St. 30'	37,0	64/74	3395
1			1		gebad. Fuss	-	60/70	3185
34	N. P.	23.	2. 48	2 Mon. 5 T.	Vor d. Vers.	37,0	60/70	3450
-			1	1	nach 1 St. 15'	36,9	60/70	3085
,	1		1	()	gebad. Fuss	-	56/65	2975
7			1	()	nach 3 St. 30'	37,0	63/73	4050
1	1				gebad. Fuss	-	58/68	3225
25	TA	0	- 48	- Mon 22 T	Vor d. Vers.	26.7	-8/68	2220
35	J. A.	9.	1. 40	2 Mon. 23 T.	nach 1 St. 15'	36,7	58/68	3,320
,	1		1	1		36,0	56/65	3070
	1		1	()	gebad. Fuss	26.6	58/68	3175
,	1		1	()	nach 3 St.	36,6	53/64	3080
					gebad. Fuss	-	58/68	3035
36	J. A.	14.	1. 48	3 Mon.	Vor d. Vers.	36,5	62/72	3465
1	1			1	nach 1 St. 15'	35,4	56/65	3125
,	1		1	()	gebad. Fuss	-	51/60	3230
,	- 1		1	()	nach 3 St.	36,3	58/68	3480
1					gebad. Fuss	-	56/65	3035
37	K. T.	16.	1 48	2 Mon. 26 T.	Vor d. Vers.	37,0	62/72	3630
31	A	Au.	3. 4	2 5101.	nach i St. 15'	36,0	59/69	3250
7	1		1	1	gebad. Fuss	30,0	64/74	3450
)			1	()	nach 3 St.	36,8	60/70	3.480
,					gebad. Fuss	30,0	62/72	3,100
9			0			-06		
38	M. M.	20.	2. 48	1 Mon. 17 T.	Vor d. Vers.	36,6	72/83	4210
,			1	1	nach 1 St. 15'	36,2	71/80	3950
7			1	()	gebad. Fuss	-	64/74	4090
,			1	()	nach 3 St. 30'	36,6	68/79	4380
	1			1	gebad. Fuss	-	60/70	3760

Fuss

Fär

1,0 1,1 1,1 1,1

0,9 0,9 0,9 0,8 1,0

1,00 1,00 1,00 1,00 1,1. 1,00 0,90 1,00

1,00 1,00 1,00 1,00 1,00 1,00

1,05 1,05 0,94 0,97 1,08

1,00 1,00 1,00 1,04 1,09

0,99 0,99 0,90 0,90 0,92

Fussbäder auf das Blutbild

Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
0	7050	21	0	0	0	0	1790	5217	21
1,08	8950	0	0 .	0	0	116	3410	5218	206
1,08	7150	100	0	0	0	0	2524	4505	21
1,13	7800	_		_	-	-	-	-	-
1,13	9500	29	0	0	0	29	2024	7390	29
1,10	7000	-		-	-	-	_	-	
0,92	12200	122	0	0	0	85	1586	10322	85
0,93	15070	45	0	0	0	0	3617	11302	106
0,95	6650	67	0	0	0	47	1264	5186	153
0,98	6050	_	-		- 1	_		-	_
0,87	7400	74	0	0	0	52	1406	5772	170
1,01	6000	-	_	-	-	-	_	-	-
0,97	12420	50	0	0	0	161	2360	9812	37
1,06	12700	0	0	0	0	508	3175	8128	889
0,97	12450	87	0	0	0	336	3772	8093	162
1,08	13800				_			-	-
1,00	8000	56	0	0	0	136	1920	5752	132
1,09	9000	_	_	-	-	-	_	-	_
1,00	10200	102	0	0	0	173	3400	6120	408
1,14	9500	29	0	0	0	29	3040	6014	380
1,08	10550	_	_		_	_	_	-	_
0,90	14700	0	0	0	0	103	4851	9702	44
1,06	13000	_	_	-	_		_	1 -	-
1,03	8300	58	0	0	0	108	3843	4175	108
1,06	9350	94	65	0	0	94	4833	3992	252
1,06	8450	59	59	0	0	169	5205	2535	423
1,05	7700	54	0	0	0	54	4466	2926	208
1,13	8750	61	0	0	0	175	4515	3665	324
1,03	8200	107	0	0	0	82	3829	3936	24
1,05	9200	184	0	0	0	368	5336	2944	368
0,94	8625	173	0	0	0	345	5003	2845	250
0,97	10000	170	0	0	0	430	5330	3770	300
1,08	11500	150	0	0	0	345	6785	3645	57
1,00	8800	150	26	0	0	88	1056	7190	29
1,09		80	. 0	0	0	56	1944	5600	32
1,06	~ ~	121	0	0	0	93	2353	6351	37
1,04	6900	48	0	. 0	0	48	918		29
1,09	7600	53	0	0	0	76	1064	6232	17
0,99		918	0	0	0	248	4415		43
0,99		724	0	0	0	333	8356	9922	39
0,90		-	-	-	_	-	-6.0	2000	
0,90		281	0	0	0	159	5612	5978	15
0,92	11450	-	_	1 -	1 -	-	-	1	1

ÜBER DIE EINWIRKUNG KALTER MILCH SOWIE KALTEN BARIUMBREIES AUF DAS PERIPHERE BLUTBILD DES SÄUGLINGS.

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Das Material umfasst insgesamt 51 Versuche.

Auf das Material verteilen sich die Versuche folgenderweise:

- A. In 36 Fällen wurde die Einwirkung eisgekühlter Milch auf das periphere Blutbild untersucht.
- B. a) in 10 Fällen wurde die Einwirkung eisgekühlten Bariumbreies auf das periphere Blutbild untersucht, ausserdem wurden Röntgenbilder des Verdauungstraktes zur Feststellung der Dauer der Magenentleerung aufgenommen.
 - b) in 5 Fällen erhielten die Säuglinge zur Kontrolle + 37° warmen Bariumbrei, es wurden dieselben Untersuchungen, wie unter Punkt a erwähnt, ausgeführt.

Ausführung der Versuche.

Sämtliche Kinder hatten zur Zeit der Versuche ein gutes Allgemeinbefinden.

In sämtlichen Fällen wurde das Gewicht bestimmt und in fast allen die Rektaltemperatur gemessen. Danach erfolgte die Blutentnahme, wie üblich durch Fersenstich. Die Blutentnahme erfolgte frühstens 4 Stunden nach der letzten Nahrungsaufnahme.

In den unter Punkt A erwähnten Versuchen wurde den Kindern ihre übliche Milchmischung, oft Muttermilch, in eisgekühltem Zustand zugeführt. Um ein Erwärmen der Milch vor dem Gelangen in den Magen zu verhindern, wurde die eisgekühlte Milch mit der Magensonde dargereicht. (Der Gummischlauch und der Trichter wurden vor dem Gebrauch im Eisschrank abgekühlt.)

Die Temperatur der Milch betrug 4—11°C, in den meisten Fällen war die T° 4—5°C. In einzelnen Fällen trat Vomitus fast sofort anschliessend auf, das Blutbild wurde jedoch auch in diesen Fällen untersucht (Versuch 5, 8, 21, 29, 36).

Die Blutbilduntersuchungen erfolgten nach Zuführung der Milch in verschiedenen Zeitabschnitten.

In den unter Punkt B erwähnten Versuchen wurde der eisgekühlte Bariumbrei nach Bestimmung des Körpergewichtes und der Blutentnahme ebenfalls mit der Magensonde zugeführt. In 10 Fällen betrug die Temperatur des Bariumbreies $3-8^{\circ}$ C, in $5+37^{\circ}$ C. Danach wurden in verschiedenen Zeitabschnitten das Blutbild untersucht und die Röntgenbilder aufgenommen.

A. ÜBER DIE EINWIRKUNG DER EISGEKÜHLTEN MILCH AUF DAS PERIPHERE BLUTBILD.

Wie schon erwähnt wurden insgesamt 36 Versuche ausgeführt. In einigen Fällen erfolgte der Versuch am selben Kinde 2 Mal, jedoch an verschiedenen Tagen.

Das Alter der Kinder schwankte zwischen 11 Tagen und 6 $^1/_2$ Monaten. Aus den Ergebnissen der Versuche geht hervor, dass das Alter keinen Einfluss auf die Blutbildveränderungen hatte.

Die Rektaltemperatur wurde in 21 der 36 Fälle gemessen. Nach Zuführung der eisgekühlten Milch sank sie überhaupt nicht oder völlig unbedeutend, um 0,1—0,3°.

In meinen Versuchen stellte ich fest, dass die zugeführte eisgekühlte Milch Veränderungen des peripheren Blutbildes hervorruft. Wie schon erwähnt waren die Veränderungen der Körpertemperatur völlig bedeutungslos.

Auffallend ist, dass der Ery-, Hb- und Leuko-Wert sich verändern.

Die Ery-Werte sinken nach Darreichung der eisgekühlten Milch in fast allen Fällen. Schon 15 Min. nach Zuführung der Milch sind die Ery-Werte bedeutend niedriger als vor dem Versuch. Gleichzeitig findet ebenfalls eine Abnahme des Hb-Gehaltes statt.

Auch die Leuko-Werte weisen Veränderungen auf, die Abnahme dominiert.

Zur deutlicheren Veranschaulichung der Veränderungen des Blutbildes führe ich die Resultate der Blutuntersuchungen in Tabellen geordnet an.

Veränderungen des Hb-Gehaltes.

TABELLE N:0 10

Anzahl der Fälle	Zeit nach Darreichung der Milch	Mittel Hb- Gehalt vor Darr. d. Milch	Mittel Hb- Gehalt nach Darr. d. Milch	Veränderuu- gen in % vom Werte zuvor
10	15 Min.	90,8	86,3	— 5
6	20 Min.	79,3	76,0	- 4.4
6	30 Min.	85.7	82,8	- 3.4
7	45 Min.	76,6	72.9	- 4.9
3	1 Stunde	83,3	75,0	10
8	1 St. 30 Min.	91,9	86,0	- 6,4
3	2 St.	79.3	76,7	- 3.4
7	3 St.	85,0	80,7	- 5,0
9	3 St. 30 Min.	90,9.	85,2	- 6.3

Zu- und Abnahme des Hb-Gehaltes in % vom Werte vor Darreichung der eisgekühlten Milch.

Wie aus der Tabelle hervorgeht, war der Hb-Gehalt schon 15 Min. nach Zuführung der eisgekühlten Milch durchschnittlich um 5 % niedriger als der Wert vor dem Versuch. In einem Fall (Versuch 10) war der Hb-Gehalt jedoch um 2,4 % höher als vor dem Versuch, diese geringe Differenz liegt jedoch im Bereich der Fehlergrenze. In Versuch 1 war der Hb-Gehalt 15 Min. nach Zuführung der Milch unverändert.

20 Min. nach Zuführung der eisgekühlten Milch ist der Hb-Mittelwert um 4,4 % niedriger als vor dem Versuch. In Versuch 16 dagegen war der Hb-Gehalt um 8 % höher als vor Darreichung der eisgekühlten Milch, dagegen war er 2 St. nach dem Versuch im selben Fall um 3,9 % niedriger als vor dem Versuch. In Versuch 11 war der Hb-Gehalt 20 Min. nach Zuführung der eisgekühlten Milch unverändert.

30 Min. nach der Milchdarreichung war der Hb-Gehalt durchschnittlich um 3,4 % niedriger als vor dem Versuch, im Versuch 18 dagegen um 3,1 % höher. Im Versuch 19 war der Hb-Gehalt unverändert.

45 Min. nach Darreichung der eisgekühlten Milch war der Hb-Gehalt durchschnittlich um 4,9 % niedriger als vor dem Versuch. Im Versuch 24 z. B. betrug die Differenz — 8 %. Dagegen war der Hb-Gehalt im Versuch 26 um 3,1 % höher als vor dem Versuch, im selben Fall war der Hb-Gehalt wiederum 2 St. nach der Milchzuführung um 6,1 % niedriger als vor dem Versuch.

Die Hb-Werte des Versuches 29 habe ich bei der Berechnung des Mittelwertes nicht mitgezählt, da ich die exakten Werte wegen dem hohen Hb-Gehalt nicht feststellen konnte (> 140).

I St. nach der Milchdarreichung wurde der Hb-Mittelwert aus den Versuchen 31, 34, 33 errechnet und war um 10 % niedriger als vor dem Versuch. Im Versuch 32 war der Hb-Gehalt dermassen hoch, dass ich die exakten Werte nicht bestimmen konnte.

I Stunde 30 Min. nach der Milchdarreichung wurde der Hb-Gehalt in 8 Fällen bestimmt und war durchschnittlich um 6,4 % niedriger als vor dem Versuch.

2 Stunden nach der Zuführung der Milch war der Hb-Gehalt, wie aus der Tabelle hervorgeht, durchschnittlich um 3,4 % niedriger als vor dem Versuch.

3 Stunden nach der Zuführung der Milch wurde der Hb-Gehalt in 8 Fällen bestimmt (Vers. 32 bei der Mittelwertberechnung nicht mitgezählt). Im Versuch 30 war der Hb-Gehalt identisch mit dem Wert vor dem Versuch. Im Versuch 27 war der Hb-Gehalt 45 Min. nach der Darreichung der Milch um 15,3 % niedriger als vor dem Versuch, 3 Stunden danach war er angestiegen, jedoch immerhin noch um 8,2 % niedriger als vor dem Versuch.

3 Stunden 30 Min. nach Darreichung der Milch war der Mitte Hb-Gehalt um 6,3 % niedriger als vor dem Versuch. Die Werte der einzelnen Versuche waren jedoch sehr variierend. Im Versuch 30 hatte der Hb-Gehalt wieder den Ausgangswert erreicht (45 Min. nach Zuführung der Milch um 8,2 % niedriger). Im Versuch 10 war der Hb-Gehalt gleichfalls identisch mit dem Werte vor dem Versuch.

Veränderungen der Ery-Werte.

Der Mittelwert der Ery betrug vor Darreichung der eisgekühlten Milch 4197000 (Max. 6880, Minim. 2655). Der Ery-Wert sinkt.

Die Veränderungen verteilen sich folgenderweise:

TABELLE N:0 11

Anzahl der Fälle	Zeit nach Darreichung der Milch	Mittelwert d. Ery vor d. Vers.	Mittelwert d. Ery nach Darr. d. Milch	Veränderung in %
10	15 Min.	4363	3991	- 8,5
6	20 Min.	3860	3616	- 6,3
6	30 Min.	3784	3698	- 2,3
7	45 Min.	3849	3462	- 10,1
4	1 Stunde	4784	4057	- 15,2
8	1 St. 30 Min.	4570	4214	- 7,8
3	2 St.	3930	3700	- 5,8
8	3 St.	4327	4102	- 5.2
10	3 St. 30 Min.	4692	4392	- 6,3

Abnahme der Ery-Werte in % vom Werte vor der Milchzuführung.

Schon 15 Min. nach Darreichung der eisgekühlten Milch ist der Ery-Wert um 8,5 % niedriger als zuvor. Im Versuch 10 ist der Ery-Wert um 10,6 % niedriger als vor dem Versuch, im Versuch 5 sogar um 16,3 %. (3 St. 30 Min. nach der Milchzuführung ist der Ery-Wert noch um c:a 8 % niedriger als vor dem Versuch.) Im Versuch 8 ist der Ery-Wert um 4,3 % niedriger als vor Darreichung der Milch (3 St. 30 Min. danach ist der Ausgangswert so gut wie erreicht).

20 Min. nach der Zuführung der Milch ist der Ery-Wert durchschnittlich um 6,3 % niedriger als vor dem Versuch, dagegen ist der Ery-Wert im Versuch 16 um 18,4 % höher als zuvor. (2 Stunden nach der Milchzuführung ist der Ery-Wert wiederum um c:a 9 % niedriger als vor dem Versuch.)

30 Min. nach der Milchdarreichung ist der Ery-Wert durchschnittlich um 2,3 % niedriger als vor dem Versuch, in 2 Fällen ist er dagegen höher (Vers. 18, 21).

45 Min. nach der Milchzuführung ist der Ery-Wert in sämtlichen Fällen niedriger als vor dem Versuch, durchschnittlich um 10,1 %.

Auch I St. nach Darreichung der Milch ist der Ery-Wert bedeutend niedriger als vor dem Versuche, durchschnittlich um 15,2 %.

Nach I Stunde 30 Min. beträgt die Differenz — 7,8 % und nach 2 Stunden durchschnittlich — 5,8 %.

3 Stunden nach Zuführung der Milch ist der Ery-Wert im Versuch 7 um 0,4 % höher als vor dem Versuch, der Mittelwert ist jedoch um 5,2 % niedriger als vor dem Versuch.

3 Stunden 30 Min. nach der Darreichung der Milch weisen die Werte keine Einheitlichkeit auf. Im Versuch 30 ist der Ery-Wert mit dem Ausgangswert identisch, in den Versuchen 10 und 36 ist er höher als vor dem Versuch.

Zusammenfassend kann man sagen, dass die kalte Milch eine Abnahme der Ery-Werte im Blute der Peripherie verursacht. Die deutlichste Abnahme stellte ich in 100 % der Fälle 45 Min. — 3 St. nach der Milchdarreichung fest. Das Maximum war 1 Stunde nach Zuführung der Milch.

Veränderungen des Färbeindexes.

Der Färbeindex vergrösserte sich in den meisten Versuchen.

Veränderungen der Leuko-Werte.

Die Veränderungen der Leuko-Werte weisen nicht eine so grosse Regelmässigkeit wie die der Hb- und Ery-Werte auf. Ihr Wert kann sowohl ansteigen als auch absinken. Die Abnahme der Leuko-Werte nach der Zuführung der eisgekühlten Milch dominiert.

Auf das ganze Material verteilen sich die Veränderungen wie aus der Tabelle 12 hervorgeht:

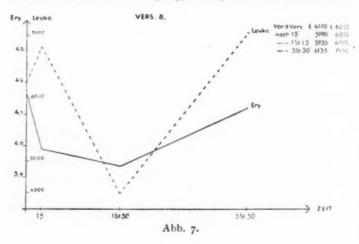
TABELLE N:0 12

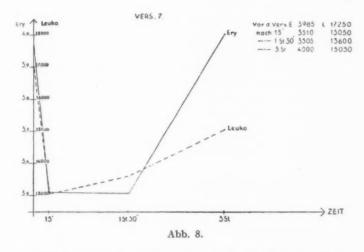
Gesamtzahl d. Fälle	Zeit nach Darreichung der Milch	Anzahl d. Fälle	Zunahme in %	Anzahl d. Fälle	Abnahme in %
10	15 Min.	4	+ 21,8	6	29,2
6	20 #	3	+ 21,4	3	- 15.5
8	45 *	3	+ 9.4	5	-11,5
4	ı St.	1	+ 11,4	3	22,4
8	1 St. 30 Min.	2	+ 5.7	6 .	- 27,6
3	2 St.			3	- 29,2
8	3 St.	5	+ 11,6	3	- 18,6
10	3 St. 30 Min.	2	+ 5.7	8	- 11,8

Ab- und Zunahme der Leuko Werte in % vom Werte vor Darreichung der eisgekühlten Milch.

Wie aus der Tabelle hervorgeht, kann der Leuko-Wert schon 15 Min. nach Zuführung der eisgekühlten Milch recht bedeutend absinken, in 6 der 10 Fälle durchschnittlich um 29,2 %. 45 Min. — 2 St. nach Darreichung der eisgekühlten Milch dominiert die Abnahme der Leuko-Werte.

Auch 3 St. 30 Min. nach Zuführung der Milch ist der Leuko-Wert in 6 der 8 Fälle um 13,1 % niedriger als vor dem Versuch.





Die Veränderungen der Ery-und Leuko-Werte haben keinen Zusammenhang. Beim Absinken der Leuko-Werte können die Ery-Werte ansteigen und umgekehrt.

Zur Veranschaulichung füge ich einige graphische Darstellungen bei. (Abb. 7, 8.)

Veränderungen des Differentialblutbildes.

Die Anzahl der weissen Blutzellen der einzelnen Zellkategorien weist verhältnismässig grosse Schwankungen auf. Eine gewisse Regelmässigkeit konnte ich in den Veränderungen der Zahl der Lymphozyten feststellen, in den meisten Fällen nahm die absolute Zahl der Ly nach Zuführung der eisgekühlten Milch ab.

Auf die einzelnen Zellkategorien verteilen sich die Veränderungen folgenderweise: die absolute Zahl der Eosinophilen und Basophilen ist gering und die Veränderungen ihrer Werte weisen keine Regelmässigkeit auf.

Auch die Veränderung der Zahl der Stabkernigen weist keine Regelmässigkeit auf. Die Anzahl der Segmentkernigen kann nach Zuführung eisgekühlter Milch sowohl steigen als auch sinken.

15 Min. nach Darreichung der Milch nimmt ihre Anzahl in der Hälfte der Fälle zu, in der anderen Hälfte ab. In Versuch 5 sinkt ihre Anzahl um fast 50 % des Wertes vor dem Versuch, 3 St. 30 Min. nach Darrelchung der Milch ist ihre Anzahl dagegen höher als vor dem Versuch. Im Versuch 35 dagegen ist die Anzahl der Segmentkernigen 1 St. 30 Min. nach Zuführung der eisgekühlter Milch um c:a 26 % höher als vor dem Versuch, 3 St. 30 Min. wiederum um 9,1 % niedriger als vor Darreichung der Milch.

Die Abnahme der Anzahl der Sg dominiert.

Auf das ganze Material verteilen sich die Veränderungen folgenderweise:

Veränderungen der Werte der Sg nach Zuführung eisgekühlter Milch (Zuund Abnahme in % vom Werte vor dem Versuch):

nach 15'-	-45 [']			
in 10	Fällen	Zunahme	um	47.5 %
D 12	2 *	Abnahme		30,2 %
nach 45'-	_1 St.			
in 7	Fällen	Zunahme	um	28,7 %
9 5	; »	Abnahme		15,1 %
nach i S	t. 30—2	St.		
in a	Fällen	Zunahme	um	24.9 %
ь (5 »	Abnahme	9	35,1 %
nach 3 S	t.—3 St.	30'		
in 7	Fällen	Zunahme	um	22,1 %
0 10))	Abnahme	9	25.7 %

Auffallend ist, dass die Zahl der Ly nach Darreichung der eisgekühlten Milch in den meisten Fällen abnimmt. In einigen Fällen sieht man schon 15 Min. nach der Zuführung der Milch niedrigere Ly-Werte, in anderen sinkt die Ly-Zahl erst später.

Die Ly-Wertveränderungen des ganzen Materiales verteilen sich wie aus der Tabelle 13 hervorgeht.

TABELLE N:0 13

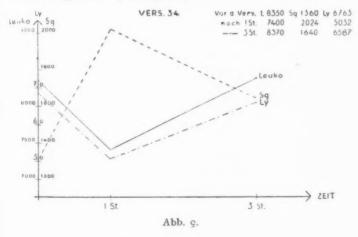
Cesamtzahl d. Fälle	Zeit nach Darreeich. d. kalten Milch	Zahl d. Fälle	Abnahme in %	Zahl d. Fälle	Zunahme in %
10	15 Min.	6	26,3	4	+ 12,1
6	20 %	4	- 31,1	2	+ 22,2
6	30 *	5	- 16,4	I	+ 2,5
8	45 *	7	- 18,5	1	+ 15,1
4	1 Stunde	3	- 30,1	-	+ 4.5
7	1 St. 30 Min.	7	- 21,8		-
3	2 St.	3	- 31,4		
8	3 St.	3	- 14,4	5	+ 8,9
9	3 St. 30 Min.	6	13,8	3	+ 10,6

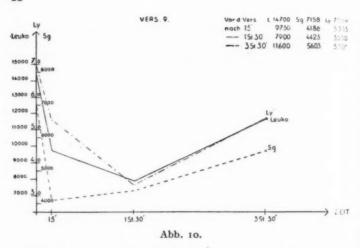
Zu- und Abnahme der Ly in % vom Werte vor Darreichung der eisgekühlten Milch.

Wie aus der Tabelle 13 hervorgeht dominiert die Abnahme der Ly-Werte deutlich ab 30 Min. nach Darreichung der eisgekühlten Milch.

Gleichzeitig können sowohl die Ly als auch die Sg absinken, oder die Sg können absinken und die Ly ansteigen und umgekehrt.

Zur besseren Veranschaulichung füge ich einige graphische Darstellungen bei. (Abb. 9, 10.)





Die absolute Anzahl der Monozyten ist verhältnismässig gering. Die eisgekühlte Milch kann im peripheren Blut sowohl ein Absinken als auch ein Ansteigen ihrer Werte verursachen.

B. ÜBER DIE EINWIRKUNG EISGEKÜHLTEN BARIUM-BREIES AUF DAS PERIPHERE BLUTBILD MIT KONTROLLE.

Die Untersuchung umfasste 15 Versuche von denen 5 Kontrollversuche mit $+37^{\circ}$ warmem Bariumbrei waren.

An einigen Kindern ist der Versuch mehrere Mal an verschiedenen Tagen ausgeführt worden. Das Alter der Versuchskinder schwankte zwischen 5 Tagen und 4 Mon. 5 Tagen.

Nach der Gewichtsbestimmung, der Blutentnahme für die Blutbilduntersuchungen und der Rektaltemperaturmessung in einigen Fällen, wurde der eisgekühlte Bariumbrei mit der Magensonde zugeführt. In verschiedenen Zeitabschnitten danach erfolgten die Blutentnahmen und Röntgenbildaufnahmen.

Wegen der geringen Anzahl der Fälle habe ich keine Mittelwert-Berechnungen ausgeführt.

Anschliessend führe ich Resultate der Untersuchungen in Gruppen geordnet an.

TABELLE N:0 14

Veränderungen der Ery-Werte und des Hb-Gehaltes I St. 30 Min. nach Zuführung eisgekühlten sowie + 37° warmen Bariumbreies

Barium brei	110 ccm kalt	110 cm + 37°	rro cem kait	80 ccm kalt	80 ccm + 37°	100 ccm kalt	110 ccm + 37°	80 ccm kalt
Ery	3,2	+ 6.5	- 13.7	- 12,4	+ 2.7	+ 15,0	+ 2,6	14.4
Ery	3620	4215	3890	4770	4335	5080 5840 4900	4250	3835
Hb Diff in %	69,	2,3	I'II —	2,0	3,3	5,9	2,0	7.7
H	1	+	Ì	1	+	++1	+	1
Hp	63/72	76/88	18/0/	88/100	78/90	102/118 108/125 102/118	88/100	67/78
Zeit	Vor d. Versuch nach I St. 30'	Vor d. Versuch nach 1 St. 30'	Vor d. Versuch nach I St. 30'	Vor d. Versuch nach 1 St. 30'	Vor d. Versuch nach r St. 30'	Vor d. Versuch nach 30' nach 1 St. 30'	Vor d. Versuch nach 1 St. 30'	Vor d. Versuch nach 1 St. 30'
Alter Gewicht	I Mon. 3 T. 2840 g	I Mon. 5 T. 2840 g	I Mon. 17 T. 2910	5 Tage 3170	8 Tage 3090	19 Tage 2460	11 Tage 2620	7. 11. 47 J. B-B. 3 Mon. 7 T.
Name	B. J.	B. J.	B. J.	R. I.	R. I.	T. A.	T. A.	J. B-B.
Datum	2. 7.47	4. 7.47	16. 7.47	2. 8.47	5. 8.47	12. 9.47	8. 9.47	7. 11. 47
N:0	н	1 8	8	4	8	10	5 a	6

Zu- und Abnahme der Ery- u. Hb-Werte in % vom Werte vor Zuführung des Bariumbreies.

Wie aus der Tabelle 14 hervorgeht sinken sowohl der Hb-Gehalt als auch der Ery-Wert nach Darreichung des eisgekühlten Bariumbreies, dagegen steigen die Werte nach Zuführung $+37^{\circ}$ warmen Bariumbreies.

Im Versuch 5 ist der Ery-Wert 30 Min. nach Darreichung des eisgekühlten Bariumbreies um 15 % höher als zuvor, dagegen ist er 1 St. 30 Min. danach, wie in den anderen Fällen, niedriger als vor dem Versuch.

Die Veränderungen der Leuko-Werte derselben Fälle verhalten sich wie aus der Tabelle 15 hervorgeht:

TABELLE N:0 15

Versuchs N:o	Name	Zeit	Leuko	Leuko Diff. in %	Barium
1	В. Ј.	Vor d. Versuch	15550	-	
		nach 1 St. 30'	17600	+ 13,2	Kalt
ı a	В. Ј.	Vor d. Versuch	14450		
		nach 1 St. 30'	15000	+ 3,8	+ 37°
3	в. J.	Vor d. Versuch	9600		
		nach 1 St. 30'	10800	+ 12,5	Kalt
4	R. I.	Vor d. Versuch	4850		
		nach 1 St. 30'	5750	+ 18,6	Kal
4 a	R. I.	Vor d. Versuch	5970		
		nach 1 St. 30'	5700	- 4.3	+ 37°
5	T. A.	Vor d. Versuch	12850		
		nach 1 St. 30'	11950	- 7,0	Kal
			12600	- 1,9	
5 a	T. A.	Vor d. Versuch	9600		
-		nach 1 St. 30'	11350	+ 18,2	+ 37°
9	J. B-B.	Vor d. Versuch	8250	-	
		nach 1 St. 30'	5650	- 3,1	Kalt

Zu- und Abnahme der Leuko Werte in % vom Werte vor Zuführung des Bariumbreies.

TABELLE N:o 16

Veränderungen der Ery u. Hb-Werte I u. 2 Stunden nach Zujührung eisgehühlten sowie + 37° warmen Bariumbreies

Barium- brei	80 ccm kalt	80 ccm + 37°	40 ccm kalt	60 ccm kalt	80 ccm + 37°	80 ccm kalt Vomitus	roo ccm kalt
Ery	- 6,1 + 6,7	+ 10,9 + 0	— 6,3 — 0,3	- 5,7	+ 20,9	0,4	- 16,2
Ery	2810 2640 3000	2560 2840 2560	2680 2510 2665	3035 2860 2960	3170 3835 3100	2815	4490
Hb	+ 3,4	++ 3.4	3,0	2,9	+ 12,9 + o	o +1	15,1
HP	50/58 48/55 51/60	50/58 51/60 50/58	57/66 55/64 55/64	58/68 58/68	02/09	53/62	80/93
Zeit	Vor d. Versuch nach 1 St. nach 2 St.	Vor d. Versuch nach 1 St.	Vor d. Versuch nach 2 St. 30'				
Alter Gewicht	2 Mon. 3090 g	I Mon. 29 T. 3090 g	4 Mon. 2780 g	4 Mon. 2 T. 2760 g	4 Mon. 4 T. 2800 g	25 T. 3910	1 Mon. 9 T. 2830
Name	J. P.	J. P.	S. R.	S. R.	S. R.	P. A.	B. J.
Datum	25. 10. 47	24. 10. 47	27. 10. 47	29. 10. 47	31. 10. 47	25. 11. 47	8. 7.47
N:0	9	6 a	7	oro	d 00	IO	61

Zu- und Abnahme der Ery u. Hb Werte in % vom Werte vor Zuführung des Bariumbreies.

Laut der Tabelle 15 dominiert 1 St. 30 Min. nach Zuführung des eisgekühlten Bariumbreies die Zunahme der Leuko-Werte. Im Fall 5 und 9 dagegen nehmen die Leuko-Werte ab.

Nach Darreichung + 37° warmen Bariumbreies können die Leuko-Werte sowohl zu- als auch abnehmen.

TABELLE N:o 17

N:o	Name	Zeit	Leuko	Leuko Diff. in %	Barium- brei
6	J. P.	Vor d. Versuch	11300		
		nach 1 St.	14650	+ 29.7	Kalt
		nach 2 St.	13530	+ 19.7	
6 a	J. P.	Vor d. Versuch	10500		
		nach 1 St.	13650	+ 30,0	+ 37°
		nach 2 St.	10900	+ 3,8	
7	S. R.	Vor d. Versuch	12300		
		nach 1 St.	12300	+ 0	Kalt
		nach 2 St.	9750	- 20,8	
8	S. R.	Vor d. Versuch	9900		
		nach 1 St.	9350	- 5,6	Kalt
		nach 2 St.	9700	- 2,0	
8 a	S. R.	Vor d. Versuch	8450		
		nach 1 St.	10650	+ 26,0	+ 37°
		nach 2 St.	8900	+ 5.3	
10	T. A.	Vor d. Versuch	10970		
		nach 1 St.	13000	+ 10,3	Kalt
2	В. J.	Vor d. Versuch	17125		
		nach 2 St. 30'	15400	- 10,0	Kalt

Leuko Diff = Zu- und Abnahme der Leuko-Werte in % vom Werte vor der Versuch.

Aus der Tabelle 16 geht hervor, dass der Ery-Wert 1 Stunde nach Zuführung des eisgekühlten Bariumbreies, ausser Versuch 10, bei dem Vomitus 10 Min. nach Darreichung des Breies auftrat, um c:a 6 % niedriger als vor dem Versuch ist. Die Veränderungen weisen eine grössere Regelmässigkeit auf als in den Versuchen, bei denen der Ery-Wert 1 St. 30 Min. nach der Zuführung des Bariumbreies bestimmt wurde. Der Hb-Wert sinkt ebenfalls, jedoch unbedeutend.

Das Alter hat keinen Einfluss auf die Ery-Wertveränderungen. In den beiden Kontrollfällen steigt der Ery-Wert.

Aus der Tabelle 17 geht hervor, dass die Leuko-Wertveränderungen auch in diesen Fällen keine Regelmässigkeit aufweisen. Ihre Werte können nach Zuführung des eisgekühlten Bariumbreies sowohl zu- als auch abnehmen. Dagegen sieht man ein Ansteigen der Leuko-Werte nach Darreichung + 37° warmen Bariumbreies.

Vergleicht man die Leuko-Werte aller Versuche so kann man feststellen, dass der Leuko-Wert in der Hälfte der Fälle ansteigt und in der anderen Hälfte absinkt.

In 4 der 5 Fälle, denen zur Kontrolle + 37° warmer Bariumbrei zugeführt wurde, stieg der Leuko-Wert und sank in 1 Fall. (Versuch 4 a, im selben Kinde verursachte der kalte Bariumbrei ein Ansteigen der Leuko-Werte.) Das Alter hatte keinen Einfluss auf die Veränderungen der Leuko-Werte.

Veränderungen des Differentialblut bildes.

Die Veränderungen des Differentialblutbildes waren äusserst variierend, auch in den Fällen denen $+37^{\circ}$ Bariumbrei zugeführt wurde.

Die Anzahl der Eosinophilen konnte nach Zuführung des eisgekühlten wie auch des $+37^{\circ}$ warmen Bariumbreies sowohl steigen als auch sinken. Eine Zunahme der Werte der Eos trat jedoch in 9 der 15 Fälle auf.

Die Basophilen waren nur in 2 Fällen nachweisbar.

Die absolute Anzahl der Stabkernigen war verhältnismässig gering. Auch ihre Anzahl konnte nach Zuführung des kalten sowie des warmen Bariumbreies sowohl steigen als auch sinken. Meistens stieg die Anzahl der Stabkernigen in den Fällen, in denen auch die Anzahl der Segmentkernigen stieg und sank beim Sinken der Segmentkernigen. In der Anzahl der Segmentkernigen kann man folgende Regelmässigkeit feststellen: der $+37^{\circ}$ warme Bariumbrei verursachte in sämtlichen 5 Fällen eine Zunahme ihrer Anzahl, nach Darreichung des eisgekühlten Bariumbreies dagegen sank die Anzahl der Segmentkernigen in 7 der 10 Versuche, durchschnittlich um c:a 19,4 $^{0}/_{0}$.

Die Veränderungen der Ly-Werte weisen keinerlei Einheitlichkeit auf. Sowohl in den Versuchen in denen eisgekühlter Bariumbrei zugeführt wurde, als auch in den Kontrollfällen, kann ihre Anzahl sowohl niedrigere als auch höhere Werte als vor dem Versuch aufweisen.

Röntgenkontrolle.

In sämtlichen 15 Fällen wurden Röntgenaufnahmen des Verdauungstraktes zur Feststellung der Dauer der Magenentleerung, ausgeführt.

Auf die einzelnen Versuche verteilen sich die Ergebnisse folgenderweise:

Versuch 1. (B. J.) 110 ccm eisgekühlten Bariumbrei Röntgenaufnahmen

1. Sofort nach Zuführung des Bariumbreies

2. Nach 45 Min.

3. » 1 St. 15 Min. »

Spuren d. Breies im Ventrikel

4. * 2 St. 30 Min.

5. 3 4 St. 15 Min. Ventrikel leer

Versuch 1 a (B. J.) 100 ccm + 37° Bariumbrei

I. Nach I St. 15 Min. Ventrikel leer

2. 9 2 St. 30 Min.

Versuch 2 (B. J.)

100 ccm eisgekühlten Bariumbrei

1. Nach 1 St. 15 Min. 10 % d. Breies im Ventrikel

2. 9 2 St. 30 Min. Ventrikel leer

Vresuch 3. (B. J.)
110 ccm eisgekühlten Bariumbrei

1. Nach 1 St. 15 Min. 5 % d. Breies im Ventrikel

2. » 2 St. 30 Min. Ventrikel leer

Versuch 4 (R. J.)

80 ccm eisgekühlten Bariumbrei

1. Sofort nach Zuführung des Bariumbreies

2. Nach 1 St. 15 Min. 30 % d. Breies im Ventrikel

3. ** 2 St. 30 Min. Spuren ** **

Versuch 4 a (R. J.)

80 ccm + 37° Bariumbrei

1. Nach 1 St. 15 Min. 30 % d. Breies im Ventrikel

2. Nach 2 St. 30 Min. Ventrikel leer

Versuch 5 (T. A.)

100 ccm eisgekühlten Bariumbrei

1. Nach 1 St. 15 Min. 20 % d. Breies im Ventrikel

Versuch 5 a (T. A.)

110 ccm + 37° Bariumbrei

1. Nach 1 St. 15 Min. 80 % d. Breies im Ventrikel

2. \$ 2 St. 30 Min. 50 % \$ \$ \$

Versuch 6 (J. P.) 80 ccm eisgekühlten Bariumbrei 1. Nach 1 St. 15 Min. Spuren d. Breies im Ventrikel

2. 3 2 St. 30 Min. 20 %

2. 9 2 St. 30 Min. Spuren d. Breies im Ventri

Versuch 6 a (J. P.)

80 ccm + 37 Bariumbrei

1. Nach 1 St. 15 Min. 20 % d. Breies im Ventrikel

2.

2 St. 30 Min. Ventrikel leer

40 ccm eisgekühlten Bariumbrei 1. Nach 2 St. 30 Min. Ventrikel leer

Versuch 7.

Versuch 8. (S. R.)
60 ccm eisgekühlten Bariumbrei
1. Nach 1 St. 30 Min. 10 % d. Breies im Ventrikel
2. * 2 St. 30 Min. 5 % * *

Versuch 8 a. (S. R.)

80 ccm + 37° Bariumbrei

1. Nach 1 St. 30 Min. 10 % d. Breies im Ventrikei

2. ** 2 St. 30 Min. Spuren ** **

80 ccm eisgekühlten Bariumbrei 1. Nach 1 St. 30 Min. 5 % d. Breies im Ventrikel 2. 0 2 St. 30 Min. Ventrikel leer

Versuch 9. (J. B-B.)

Versuch 10. 80 ccm eisgekühlten Bariumbrei 1. Nach 1 St. 20 % d. Bariumbreies im Ventrikel.

An Hand der Röntgenuntersuchungen konnte ich nicht feststellen, dass der eisgekühlte Bariumbrei eine verlangsamte Entleerung des Magens verursacht.

In Versuch 4 und 4 a hatten sowohl nach Zuführung des eisgekühlten wie auch des + 37° warmen Bariumbreies 70 % den Ventrikel 1 St. 15 Min. nach Darreichung des Breies passiert.

Im Versuch 5 hat I St. 15 nach Zuführung des Bariumbreies 80 % den Ventrikel passiert, im Versuch 5 a hat in derselben Zeiteinheit 20 % den Ventrikel passiert, im selben Versuch ist 2 St. 30 Min. nach Zuführung des warmen Bariumbreies noch 50 % im Ventrikel, in derselben Zeiteinheit haben im Versuch 5 dagegen schon 80 % den Ventrikel verlassen.

Auch in den Versuchen 6 und 6 a sieht man, dass im ersteren der kalte Bariumbrei den Ventrikel schneller verlässt als der warme.

In den Versuchen 8 u. 8 a entleert sich der Ventrikel sowohl nach Zuführung des kalten als auch des warmen Bariumbreies gleich schnell.

Zusammenfassung.

Insgesamt führte ich 51 Versuche aus, um festzustellen, ob die eisgekühlte Milch sowie eisgekühlter Bariumbrei (mit einer Kontrolle in 5 Fällen) auf das periphere Blutbild einwirken. Die eisgekühlte Milch sowie der Bariumbrei wurden mit der Magensonde zugeführt.

Die Einwirkung auf die Rektaltemperatur war unbedeutend. In sämtlichen Fällen wurde der Versuch frühstens 4 Stunden nach der letzten Nahrungszufuhr ausgeführt.

A. In 36 Fällen untersuchte ich die Einwirkung der eisgekühlter Milch auf das periphere Blutbild.

In sämtlichen Fällen fand eine Abnahme des Hb-Gehaltes und der Ery-Werte statt. Der Hb-Gehalt war 15 Min. nach Zuführung der eisgekühlten Milch durchschnittlich um 5 % niedriger als zuvor. Die niedrigsten Werte konnte ich I—I St. 30 Min.

nach Zuführung der Milch feststellen, resp. 10,0 u. 6,4 % niedriger als vor der Versuch. $3^{1}/_{2}$ Stunden nach Darreichung der Milch war der Ausgangswert noch nicht erreicht worden.

Der Ery-Wert wies ein deutlicheres Absinken auf. Die grössten Differenzen im Vergleich zum Ausgangswert könnte ich 45 Min. — 2 St. nach Zuführung der kalten Milch feststellen. Die Ery-Werte hatten ihren Ausgangswert 3 ½ St. nach Zuführung der Milch noch nicht erreicht.

Die Leuko-Werte wiesen keine Regelmässigkeit auf. Ihre Anzahl konnte durch den Kältereiz sowohl sinken als auch steigen. Eine Abnahme der Leuko-Werte dominierte jedoch und war am stärksten 1—3 St. nach Zuführung der eisgekühlten Milch, um 18,6—29,2 % niedrigere Werte.

Das Differentialblutbild wies ebenfalls völlig unregelmässige Veränderungen der absoluten Werte der weissen Blutzellen der einzelnen Zellkategorien auf. Gewissermassen dominierte die Abnahme der Zahl der Lymphozyten. 45' — 2 St. nach Zuführung der Milch fand in fast 100% der Fälle eine Abnahme der Ly-Werte um 18,5—31,0% vom Werte vor dem Versuche statt. Auch die Anzahl der Segmentkernigen nahm in zahlreicheren Fällen ab, die Veränderung ihrer Anzahl war jedoch nicht so deutlich wie die der Lymphozyten.

B. In 10 Fällen untersuchte ich die Einwirkung eisgekühlten Bariumbreies auf das periphere Blutbild, in 5 Fällen wurde eine identische Untersuchung über die Veränderungen nach Zuführung + 37° warmen Bariumbreies ausgeführt. In sämtlichen Fällen erfolgten Röntgenaufnahmen des Verdauungstraktes.

Auch in diesen Untersuchungen konnte ich ähnliche Veränderungen des Blutbildes wie in den unter Punkt A genannten Versuchen feststellen.

Der warme Bariumbrei verursachte kein Absinken der Ery u. Hb-Werte, sie stiegen im Gegenteil an.

In den Röntgenaufnahmen konnte ich nicht feststellen, dass der kalte Bariumbrei eine verzögerte Entleerung des Magens hervorrufe; in einigen Fällen entleerte der Magen sich nach Zuführung des kalten Bariumbreies schneller als nach dem warmen.*

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^{*} Die Kasuistik der Versuche der Gruppe VIII B ist in der Universitätsbibliothek zu Helsingfors deponiert.

TABELLE
Cher die Einwirkung kalter

N:o	Name	Da	atum	Alter	Zeit	T°	Hb	Ery per mm
1	Y. K.	24	3. 47	6 ½ Mon.	Vor d. Vers.	_	74/86	4330
•	1.,10	-4.	3. 41	/2	nach 15'	-	74/86	4260
2	т. н.	14.	4- 47	2 ½ Mon.	Vor d. Vers.	_	58/68	3115
_			7 17	/-	nach 15'	_	56/65	2820
3	I. H.	21.	4. 47	3 Wochen	Vor d. Vers.	-	110/128	5150
					nach 15'	_	106/123	4600
4	K. M.	23.	4. 47	4 Mon. 23 T.	Vor d. Vers.	36,6	60/70	3390
					nach 15'	36,3	58/68	3130
5	M. M.	16.	2. 48	1 1/2 Mon.	Vor d. Vers.	36,6	88/102	4835
_					nach 15'	36,6	76/88	4045
					nach 3 St. 30'	36,6	84/97	4410
6	V. K-H.	I.	3. 48	1 Mon. 3 W.	Vor d. Vers.	36,8	108/125	5715
	1				nach 15'	36,8	103/119	
					nach 1 St. 30'	36,8	100/116	5140
					nach 3 St.	36,8	100/116	5370
7	K. K.	I.	3. 48	3 Mon. 8 T.	Vor d. Vers.	37,0	66/77	3985
					nach 15'	36,8	64/74	3510
					nach 1 St. 30'	37,0	64/74	3505
					nach 3 St.	37,0	66/77	4000
8	J. A.	10.	3. 48	4 Mon. 23 T.		36,9	68/79	4170
					nach 15'	36,8	64/74	3990
					nach 1 St. 30'	36,8	62/72	3935
					nach 3 St. 30'	36,8	65/75	4135
9	K. E.	8.	3. 48	3 Mon. 20 T.	Vor d. Vers.	36,8	78/90	4875
					nach 15'	36,7	72/83	4165
		I			nach 1 St. 30'	36,8	70/81	4180
					nach 3 St. 30'	36,8	74/86	4270
10	K. E.	10.	3. 48	3 Mon. 22 T.	Vor d. Vers.	36,8	72/83	4065
					nach 15'	36,7	73/85	4040
					nach i St. 30'	36,7	70/81	3905
					nach 3 St. 30'	36,8	72/83	4295
11	K. Y.	27.	3. 47	6 Mon. 17 T.	Vor d. Vers.	-	74/86	4110
					nach 20'	-	74/86	3990
12	K. L.	27.	3. 47	6 Mon.	Voj d. Vers.	36,8	84/97	5175
					nach 20'	36,7	71/82	4000

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N:0 18 Milch auf das periphere Blutbild

Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
1,00	6900	138	48	48	0	138	1904	4554	70
1,02	6750	88	0	68	0	115	1992	4319	68
1,09	9320	261	0	0	0	1118	2265	5527	149
1,12	7925	159	0	0	Ó	634	2140	4754	238
1.24	14700	147	147	0	0	1470	5660	6688	588
1,33	18350	275	92	0	0	2294	8441	6973	27
* * * *	5700	262	0	0	0	245	1253	3727	270
1,04	6700	154	40	0	0	442	1843	4020	20
		-66				-66	0 -		
1,06	16600	166	0	0	0	166 66	4482	11620 6993	16
1,07	17000	151 51	0	0	0	119	2079 5780	10540	51
.,									
1,09	9850	69	0	0	0	59	2561	7092	6
1,12	12500	163	0	0	0	125	3837	8037	33
1,13	9600	0	0	0	0	96	3264	5952	28
1,01	11250	45	0	0	o	34	3488	7537	14
0,91	17250	690	0	0	0	173	3916	12074	39
1,05	13050	431	0	0	0	104	2780	9435	30
1,05	13600	177	0	0	0	95 105	3577 2408	12235	32
0,96	15050	131	0		0	105	2400	12233	13
0,95	6250	19	0	0	0	19	1938	4115	16
0,94	6850	0	0	0	0	69	1507	5205	6
0,92	4500	14	0	0	0	63	1215	3164	6
0,91	7150	21	0	0	0	21	1735	5220	14
0,93	14700	147	0	0	0	191	7158	7056	14
1,00	9750	98	0	0	o	127	4188	5333	
0,96	7900	24	0	0	0	103	4423	3350	
10,1	11600	151	0	0	0	545	5603	5301	
1,02	11600	35	0	0	0	197	4408	6960	
1,06	7150	21	0	0	0	93	2682	4261	9
1,03	9300	_	_	-	-	_	_	-	
0,98	8800	_	_	_		-	_	_	_
1,02	7550	53	0	0	0	302	1284	5284	62
1,06	7400	23	0	0	0	237	1006	5964	17
0,94	14650	1216	44	0	0	337	1172	11398	48
1,02	10600	774	0	0	0	774	1251	7589	21

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N:o	Name	Datum		Alter	Zeit	To	Hb	Ery per mm
13	K. L.	28.	3. 47	6 Mon. 1 T.	Vor d. Vers.		72/83	4010
-5			5 11		nach 20'	-	68/79	3510
14	н. т.	II.	4. 47	2 Mon. 25 T.	Vor d. Vers.	_	58/68	3170
					nach 20'	-	55/64	2950
15	A. N.	25.	5. 47	1 ½ Mon.	Vor d. Vers.	36,8	58/68	2945
					nach 20'	36,7	55/64	2800
					nach 3 St.	36,8	55/64	2795
16	S. P.	25.	5. 47	4 Mon.	Vor d. Vers.	_	67/78	3750
					nach 20'	_	71/82	4445
					nach 2 St.	_	63/73	3420
17	Н. Т.	29.	3. 47	2 1/2 Mon.	Vor d. Vers.	_	66/77	3560
-,			0 11	/2	nach 30'	-	62/72	3200
18	н. т.	6.	4. 47	5 Mon. 7 T.	Vor d. Vers.	_	55/64	2655
					nach 30'	-	57/66	2910
19	S. S.	8.	4. 47	II T.	Vor d. Vers.	37,0	90/104	4050
					nach 30'	36,8	90/104	4040
20	M. S.	8.	4. 47	1 Mon. 6 T.	Vor d. Vers.	_	83/96	4640
					nach 30'	-	80/93	4300
					nach 2 St.		82/95	4455
21	J. A.	9.	1. 48	2 Mon. 23 T.	Vor d. Vers.	36,7	67/78	3085
					nach 30'	36,4	66/77	3130
					nach 2 St. 30'	36,7	61/72	3035
22	Y-M. H.	2.	2. 48	3 Mon.	Vor d. Vers.	36,5	82/95	4725
					nach 30'	36,3	73/85	4550
					nach 3 St. 30'	36,4	72/83	4395
23	K. Y.	26.	3. 47	5 Mon. 16 T.	Vor d. Vers.	_	64/74	3705
					nach 45'	_	62/72	3630
24	V. P.	9.	4- 47	5 Mon. 19 T.	Vor d. Vers.	_	76/88	4350
					nach 45'	_	70/81	3775
25	н. т.	16.	4. 47	3 Mon.	Vor d. Vers.	-	60/70	3010
					nach 45'	_	57/66	2875

Milch auf das periphere Blutbild

Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
1,03	11950	873	0	0	0	394	1506	8783	39
1,12	10850	792	0	0	0	250	2147	7053	608
1,09	5700	34	17	0	0	331	912	4275	13
1,09	9800	128	0	0	0	1205	2352	5723	392
1,17	8200	82	0	0	o	82	4346	3690	(
1,15	8850	27	27	0	0	27	5778	2947	4
1,16	8700	35	26	0	0	87	5246	3306	
1,04	8200	82	0	0	0	123	1353	6601	4
0,93	8300	83	0	0	0	141	1386	6582	10
1,07	8050	56	81	0	0	217	2117	5498	8
1,09	6750	0	0	0	0	1033	1053	4623	4
1,10	5800	209	0	0	0	928	1543	2929	19
1,20	9850	30	0	0	0	424	985	8155	25
1,15	9000	99	0	0	0	396	891	8019	49
1,28	10250	51	0	0	0	615	2973	6560	5
1,30	9500	143	48	0	0	855	1757	6222	47
1,04	11050	55	0	0	o	1105	3978	5912	
1,09	9150	46	0	0	0	641	3157	5260	4
1,06	4650	0	0	0	0	605	1162	2650	23
1,26	10800	184	32	0	0	108	4212	5400	86
1,24	7600	228	23	0	0	152	2964	3093	114
1,20	6200	105	0	0	0	248	2170	3243	43
1,00	10150	61	30	0	o	172	2307	7511	7
0,93	10800	108	0	0	0	216	2700	7700	7
0,90	10000	100	0	0	0	100	2700	7100	10
1,00	5150	52	0	0	o	52	1560	3398	8
1,00	6250	63	19	0	19	125	2562	3312	15
1,01	12500	38	125	0	0	1075	3162	7937	16
1,01	10350	62	311	0	52	1346	2949	5588	34
1,16	9200	120	0	0	0	1224	2686	4931	23
1,15	9500	95	0	0	0	1615	3705	3800	28

Milch

Färl:

0,9

I,0 I,0

0,9 0,9 0,9 1,0 1,0 1,0

I,C

1,2 1,2 1,0 1,0

1,0 1,0 1,0 1,0

1,0

N:o	Name Datum		Alter	Zeit	T°	НЬ	Ery per mn	
26	N. A.	2.	6. 47	1 Mon. 23 T.	Vor d. Vers.	_	57/66	3400
		-	47	3	nach 45'	_	58/68	3:30
					nach 2 St.	_	53/62	3- 25
27	N. P.	2.	2. 48	1 ½ Mon.	Vor d. Vers.	37,0	73/85	4095
					nach 45'	37,0	62/72	3,180
					nach 3 St.	37,0	67/78	3050
28	J. J.	5.	2. 48	3 Mon. 19 T.	Vor d. Vers.	37.0	67/78	4030
					nach 45'	37,0	60/70	3255
					nach 3 St.	37,0	62/72	3745
29	V. J-J.	9.	2. 48	15 T.	Vor d. Vers.	36,9	> 140	6110
					nach 45'	36,4	> 140	6320
					nach 3 St. 30'	36,8	140	5475
30	V. H-K.	8.	3. 48	2 Mon. 7 T.	Vor d. Vers.	37.1	76/88	4355
					nach 45'	37,0	70/81	4190
					nach 1 St. 30'	37,1	74/86	4245
					nach 3 St. 30'	37.1	76/88	4355
31	P. R.	10.	1. 48	3 Mon. 7 T.	Vor d. Vers.	_	69/80	3795
	1				nach 1 St.	-	66/77	3404
					nach 3 St.	_	69/80	3730
32	J. J.	2.	2. 48	28 T.	Vor d. Vers.	37.2	> 140	6880
					nach 1 St.	37,1	120/139	5 500
					nach 3 St.	37.2	122/142	5740
33	N. P.	3.	2. 48	1 Mon. 16 T.	Vor d. Vers.	37.4	76/88	4290
-					nach 1 St.	37.4	65/75	3750
					nach 3 St. 30'	37.4	67/78	3830
34	Y-M. H.	4.	2. 48	3 Mon. 3 T.	Vor d. Vers.	36,8	71/82	4170
					nach 1 St.	36,8	63/73	3515
					nach 3 St.	36,8	67/78	3785
35	J. J.	9.	2. 48	1 Mon. 4 T.	Vor d. Vers.	36,9	108/125	6200
-					nach 1 St. 30'	37,0	100/116	5680
					nach 3 St. 30'	37,0	97/113	5550
36	F. V.	13.	2. 48	1 Mon.	Vor d. Vers.	36,8	58/68	3195
				3	nach 1 St. 30'	36,8	52/62	3120
					nach 3 St. 30'	36,8	55/64	3210

Milch auf das periphere Blutbild

Färbe- index	Leuko per mm³	Eos	Bas	Myeloz	Juv	St	Sg	Ly	Мо
0.97	9300	65	47	0	0	279	2418	6258	233
	8650	130	43	0	0	173	3114	5103	87
0,97	7500	0	0	0	0	263	2513	4724	C
0171	, ,								
1,04	10300	72	0	0	0	103	2781	7313 8418	31
1,07	11225	0	0	0	0	146 86	2436		225
1,06	6550	0	0	0	0	00	1163	5305	46
0,91	6350	19	0	0	0	128	1441	4552	210
0,93	5950	60	0	0	0	60	1725	3986	HIG
0,97	6000	0	0	0	0	78	1200	4680	42
		0	0	0	0	137	4009	6330	74
	10550	0	0	0	0	204	4488	5406	102
_	10200	0	0	0	0	72	3416	6800	62
_	10350	U				/-	34		
1,01	12100	85	0	0	0	157	3509	8264	8
0,95	9800	29	0	0	0	127	2842	6762	6
1,02	9700	97	0	0	0	126	2590	6790	97
1,01	10200	133	0	0	0	133	2448	7486	(
1,06	7000	21	0	0	0	140	2359	4319	161
1,13	7800	55	0	0	0	211	2753	4524	257
1,08	7800	23	0	0	0	156	2551	4859	211
	8450	0	0	0	0	85	2172	5939	254
1,25	5000	0	0	0	0	65	1385	3350	200
1,24	9250	0	0	0	0	65	1203	7704	278
				0	0	166	2145	7312	9
1,03	9750	29	0	0	0	136	2080	5600	10
1,00	9125	24	56 55	0	0	155	2464	6387	6.
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	3-23		33						
1,00	8350	0	0	0	0	84	1360	6763	16
1,03	7400	0	74	0	0	96	2024	5032	17
1,04	8370	0	25	0	0	84	1649	6587	2.
1,00	9700	0	0	0	0	97	2164	7275	19
1,02	10300	0	31	0	0	206	2719	7138	201
10,1	7650	0	0	0	0	77	1966	5530	7
1,08	8000	0	0	0	0	56	2024	5656	18.
1,00	6720	0	0	0	0	67	1902	4462	22
1,00	7995	0	0	0	0	105	1944	5808	13

ALLGEMEINE BESPRECHUNG

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Die Anschauungen der verschiedenen Forscher über den Einfluss thermischer Reize, insbesondere der Kälte, auf das periphere Blutbild und Blutgefässsystem sind sehr variierend.

Zahlreiche Forscher sehen durch thermische Reize verursachte Veränderungen der Gefässweite als Ursache der Veränderungen des Blutbildes an. Auch die Anschauungen, ob die neurovegetative Gefässregulation zentral oder autonom geregelt wird, sind nicht einheitlich. Mehrere Autoren nehmen an, dass die endokrinen Drüsen, insbesondere die Nebennieren, hierbei eine bedeutende Rolle spielen.

Vejlens nimmt an, dass bei veränderter Gefässweite Verschiebungen der roten wie auch der weissen Blutkörperchen, insbesondere der letzteren, stattfinden und dadurch Pseudoleukozytosen und Leukopenien entstehen. Hertzman und Roth haben den Einfluss der Kälteeinwirkung auf das periphere Blutgefässgebiet studiert und stellten in Versuchen fest, dass bei lokaler Kälteeinwirkung im ausgesetzten Hautgebiet erst eine Konstriktion, danach eine Dilatation mit darauffolgender Konstriktion der Blutgefässe erfolgt. Bei Fingerbädern erfolgte eine reflektorische ähnliche Reaktion am Kontrollfinger der selben oder anderen Hand.

Nach HERLITZ fehlt beim Neugeborenen die konsensuelle Hautgefässreaktion die man beim Erwachsenen nachgewiesen hat.

THOLEZAN, BROWN, SEQUARD haben festgestellt, dass bei lokalem Wärmeentzug konsensuelle Hautgefässreaktionen auftreten die nicht nur auf die Körperoberfläche, sondern im beschränktem Masse auch auf die Blutgefässe der inneren Organe, einwirken.

ALDENHOVEN, MÜLLER, PETERSEN sehen ein splanchnoperipheres Gleichgewicht für wahrscheinlich an. Müller konnte

feststellen, dass eine Erweiterung er Splanchnicusgefässe gleichzeitig eine Verengerung der Blutgefässe der Peripherie verursacht.

FALUDI behauptet, dass lokale thermische Reize keine Veränderung des Blutbildes der Peripherie verursachen.

In meinen Versuchen wollte ich feststellen, wie sowohl lokale als auch den ganzen Körper treffende Kälteeinwirkung, auf das periphere Blutbild des Säuglings einwirkt.

Als Einleitung führte ich Tierversuche aus und konnte feststellen, dass ein kürzere oder längere Zeit dauernder Kältereiz ein bedeutendes Absinken der Körpertemperatur und der Erythrozyten (Ery), Hämoglobin (Hb) und Leukozyten (Leuko) Werte verursacht. Die deutlichste Abnahme der Ery- und Hb-Werte konnte ich 15 Minuten nach dem Kältereiz feststellen, dagegen die niedrigsten Leuko-Werte 30—40 Minuten nach dem Kältereiz.

Das Material umfasste 30 Versuche. In 11 Fällen untersuchte ich auch das Herzblut, die Ery-und Hb-Werte sanken nach dem Kältereiz stärker, die Leuko-Werte gleich stark wie im peripheren Blut. Die Werte der Lymphozyten und Segmentkernigen sanken im peripheren- und Herzblut.

Auch Nedzel hat in Tierversuchen festgestellt, dass eine Abkühlung von Hunden ein Sinken der Leuko-Werte verursacht.

In 17 Fällen untersuchte ich die Veränderungen des peripheren Blutbildes von Säuglingen, deren Körpertemperatur durch kalte Bäder gesenkt worden war.

Auch in diesen Versuchen stellte ich ein Absinken der Eryund Hb-Werte fest, dagegen stiegen die Leuko Werte in 15 von 17 Fällen. Die Ly-und Sg-Werte stiegen ebenfalls in fast allen Fällen.

Man könnte annehmen, dass die Kälteeinwirkung mit folgender Konstriktion der Kapillaren ein Abwandern der Ery aus der Peripherie in Depots verursacht. Eventuell könnte man annehmen, dass die Kälteeinwirkung eine Herabsetzung des Stoffwechsels verursacht, und der verringerte O₂ Bedarf der Gewebe die Abwanderung der Ery in Depots hervorruft. Eventuell könnte man auch an eine Beeinflussung der hämopoetischen Systeme denken.

REINEBOTH und KOHLHARDT stellten an Hand von Tierversuchen fest, dass bei einer Abkühlung von Kaninchen in den meisten Fällen eine Abnahme der Ery-Werte, mit bedeutendem Absinken des Hb-Gehaltes, stattfindet. Sie sehen als Ursache eine Schädigung der Blutzellen mit Untergang der Erythrozyten an.

WINTERNITZ, KNÖPFELMACHER und BREITENSTEIN stellten fest, dass sofort nach kalten Bädern bei Erwachsenen eine Erhöhung der Hb- und Ery-Werte stattfindet. KNÖPFELMACHER konnte $^{1}/_{2}$ Stunde nach dem Bade eine Abnahme feststellen, als Ursache sieht er eine veränderte Verteilung der Blutkörperchen an.

FRIEDLÄNDER beobachtete, dass eine anhaltende Kälteeinwirkung eine Abnahme der Erythrozyten und Zunahme der Leukozyten im peripheren Blut verursacht, auch er nimmt an, dass es sich um eine veränderte Verteilung der Blutkörperchen handelt.

Zahlreiche amerikanische Forscher: Selve, Hartman, Cannon, Querido, Crosby, Brownell u. a. haben sich mit den Problemen des Einflusses der Nebennieren bei thermischen und anderen Reizen beschäftigt.

Selve sieht es als eine der wichtigsten Aufgaben der Nebennieren an, bei schädlichen Einflüssen ein Gleichgewicht herzustellen. Selve stellte fest, dass z.B. Kälte ein Stimulus ist, der eine sogenannte »Alarm reaction» hervorruft, die auch auf das Blutbild einwirkt.

SELYE und DALTON führten Versuche aus und konnten während der »Alarm reaction» eine polymorphonucleäre Leukocytosis und Abnahme der Ery-Werte beobachten (als Reiz benutzten sie Formaldehyd Injektion und körperliche Anstrengung).

Es wäre denkbar, dass die Kälte eine Reizung der Nebennieren mit Entstehung der Alarmreaktion verursacht, und dass man die Veränderungen des Blutbildes damit erklären kann.

Zur näheren Aufklärung der Veränderungen des Blutbildes müssten noch weitgehende Untersuchungen ausgeführt werden.

Bei den Versuchen zur Feststellung der Einwirkung lokalen Kältereizes, hervorgerufen durch kalte Fussbäder eines Beines, konnte ich feststellen, dass der Ery- und Hb-Wert sowohl im Blute der der Kälte ausgesetzt gewesenen Extremität, wie auch der ungebadeten Extremität, vorübergehend absinkt. $3^{1/2}$ Stunden nach dem Kältereiz war der Ausgangswert im Kontrollblut wieder erreicht, im Blute des Versuchsbeines immerhin noch um 6,2 % niedriger als vor dem Versuch. Die niedrigsten Ery-Werte konnte ich $1^{1/2}$ Stunden nach dem Fussbade feststellen, die Ery-Werte des Versuchsbeines waren niedriger.

Der lokale Kältereiz wirkte völlig unbedeutend auf die Körpertemperatur ein.

Eventuell handelt es sich um eine Abwanderung der Ery in Depots. Die Veränderungen der Leuko-Werte wiesen in meinen Versuchen keine Einheitlichkeit auf. Im Kontrollblut konnte der Leuko-Wert z. B. erst absinken und dann ansteigen und umgekehrt, im selben Fall und in der selben Zeiteinheit, konnte man im Blute des Versuchsbeines dagegen entgegengesetzte Veränderungen beobachten. Im grössten Teil der Versuche war der Leuko-Wert 3 Stunden 30 Minuten nach dem Kältereiz im Kontrollblut niedriger und im Blute des Versuchsbeines höher als vor dem Kältereiz.

Es ist schwer zu sagen wodurch diese Veränderungen hervorgerufen werden. Man könnte annehmen, dass es sich nur um Verteilungsveränderungen handelt, eventuell finden Permeabilitätsveränderungen der Gefässwand statt.

Bei den Untersuchungen des Differentialblutbildes habe ich das Hauptgewicht auf die Veränderungen der Zellwerte des Kontrollblutes gelegt. Im grössten Teil der Fälle nahm die Zahl der Ly ab, die Zahl der Sg nahm dagegen zu.

Petersen und Müller, E. F., führten Versuche aus, um festzustellen ob das Trinken von kaltem oder warmem Wasser das periphere Blutbild beeinflusst. An Hand der Versuche stellten sie fest, dass ein splanchnoperipheres Gleichgewicht vorhanden ist. Ihrer Ansicht nach verursacht das kalte Wasser eine Zunahme und das warme Wasser eine Abnahme der Leuko der Peripherie.

In meinen 51 Versuchen mit Säuglingen konnte ich feststellen, dass nach Zuführung kalter Milch und kalten Bariumbreies mit der Magensonde, die Körpertemperatur nicht oder unbedeutend beeinflusst wird. Im Blutbild traten bedeutende Veränderungen auf. Es erfolgte eine Abnahme der Ery-und Hb-Werte, erstere sanken bedeutender ab. In fast allen Fällen waren der Ery-und Hb-Ausgangswert nach 3—3 ¹/₂ Stunden noch nicht erreicht. Die Veränderungen der Leuko-Werte wiesen dagegen nicht die Regelmässigkeit die MÜLLER und PETERSEN beschrieben haben auf. Ihrer Ansicht nach müsste die kalte Milch wie erwähnt eine Zunahme der Leuko-Werte des Blutes der Peripherie verursachen. In meinen Versuchen dominierte 15 Minuten sowie 45 Minuten—3 Stunden nach Zuführung der eisgekühlten Milch eine Abnahme der Leuko-Werte. 3 ¹/₂ Stunden nach Zuführung der Milch war der Ausgangswert in fast allen Fällen noch nicht erreicht, sondern durchschnittlich um 11,8 % niedriger als vor dem Versuch.

Die Zahl der Ly und Sg nahm in den meisten Fällen nach Zuführung der eisgekühlten Milch ab. Die Versuche mit Zuführung eisgekühlten Bariumbreies (mit Berücksichtigung der Ventrikelentleerung) bestätigten die Tatsache, dass die Ery-und Hb-Werte abnehmen, auch in diesen 10 Fällen wiesen die Leuko-Wert Veränderungen keine Regelmässigkeit auf.

Auf Grund der Resultate meiner Versuche nehme ich an, dass ein splanchnoperipheres Gleichgewicht scheinbar vorhanden ist.

An Hand meiner Versuche konnte ich feststellen, dass sowohl lokale wie auch den ganzen Körper treffende Kälteeinwirkung regelmässig eine Senkung der Ery-und Hb-Werte, ersterer bedeutender, verursacht. Die Leuko-Werte dagegen wiesen variierende Veränderungen auf.

Da mein Material klein ist und noch weitgehende hämatologische Untersuchungen ausgeführt werden müssen, sehe ich mich nicht im Stande beweisende Ursachen der Veränderungen des Blutbildes angeben zu können.

Die Frage, ob es sich nur um eine veränderte Verteilung der Blutkörperchen handelt und ob die hämopoetischen Organe und die Nebenniere eine Rolle spielen, bleibt offen und erfordert noch weitgehende Untersuchungen.

ZUSAMMENFASSUNG

An Hand des Materials, das 30 Tierversuche und 109 Versuche mit Säuglingen umfasst, konnte festgestellt werden, dass sowohl lokale wie auch den ganzen Körper treffende (mit Senkung der Körpertemperatur) Kältereize recht bedeutende Veränderungen des Blutbildes hervorrufen.

1) In den mit Meerschweinchen ausgeführten Tierversuchen wurde festgestellt, dass bei Senkung der Körpertemperatur in allen 30 Fällen eine Abnahme der Erythrozyten- Hämoglobinund Leukozytenwerte, sowohl im Herz- als auch im peripheren Blut, stattfindet. Durchschnittlich sank der Erythrozytenwert im peripheren Blut um 10,8 % vom Werte vor dem Versuch, im Herzblut war die Abnahme bedeutender. Der Hämoglobingehalt sank nicht so stark ab. Der Leukozytenwert sank im peripheren und Herzblut fast gleich stark, durchschnittlich um 38,6 %.

Im Differentialblutbild konnte in fast allen Fällen eine Abnahme der Zahl der Segmentkernigen und Lymphozyten festgestellt werden.

2) In 17 Fällen wurde die Einwirkung kalter Vollbäder auf das periphere Blutbild des Säuglings untersucht. Die Dauer der Bäder betrug 8—15 Minuten und die Temperatur des Badewassers 9—17° C. Die Körpertemperatur sank durchschnittlich um 15,2 %. Das Alter der Säuglinge schwankte zwischen 12 Tagen und 5 ½ Monaten. Unabhängig vom Alter und kleineren Variierungen der Temperatur des Körpers sanken der Erythrozytenwert und Hämoglobingehalt in sämtlichen Fällen. Der Leukozytenwert dagegen stieg in fast allen Fällen.

An einzelnen Kindern wurde der Versuch oft mehrere Mal ausgeführt, in identischen Verhältnissen und Zeiteinheiten nach dem Bade konnte die Abnahme der Erythrozyten- und Hämo-

globinwerte stark variieren, ähnlich verhielt sich die Zunahme der Leukozytenwerte.

Die absolute Zahl der Segmentkernigen und Lymphozyten stieg in fast allen Fällen.

3) In 36 Versuchen wurde die Einwirkung lokalen Kältereizes, hervorgerufen durch kalte Fussbäder, auf das periphere Blutbild untersucht. In den Versuchen wurde ein Bein bis zum Knie einem kalten Bade von 5—6° C ausgesetzt. Die Veränderungen der Körpertemperaturen waren unbedeutend. Das Blut, sowohl des Versuchs- als auch Kontrollbeines, wurde nach dem Kältereiz untersucht.

Auch in diesen Versuchen konnte ein Absinken der Erythrozytenwerte und des Hämoglobingehaltes festgestellt werden. Das Blut des Versuchsbeines wurde frühestens I Stunde 15 Minuten nach dem Kältereiz untersucht. Im Kontrollblut konnten schon 30 Minuten nach dem Fussbade durchschnittlich 9 % niedrigere Werte als vor dem Versuch nachgewiesen werden. Die niedrigsten Erythrozytenwerte wurden I Stunde 30 Minuten nach dem Fussbade festgestellt, und zwar niedrigere im Blute der gebadeten Extremität. 3 Stunden 30 Minuten nach dem Fussbade war der Ausgangswert noch nicht erreicht, es dominierten niedrigere Leukozytenwerte als vor dem Versuch.

Im Differentialblutbild wiesen die Veränderungen der Anzahl der Lymphozyten und Segmentkernigen keine Regelmässigkeit auf.

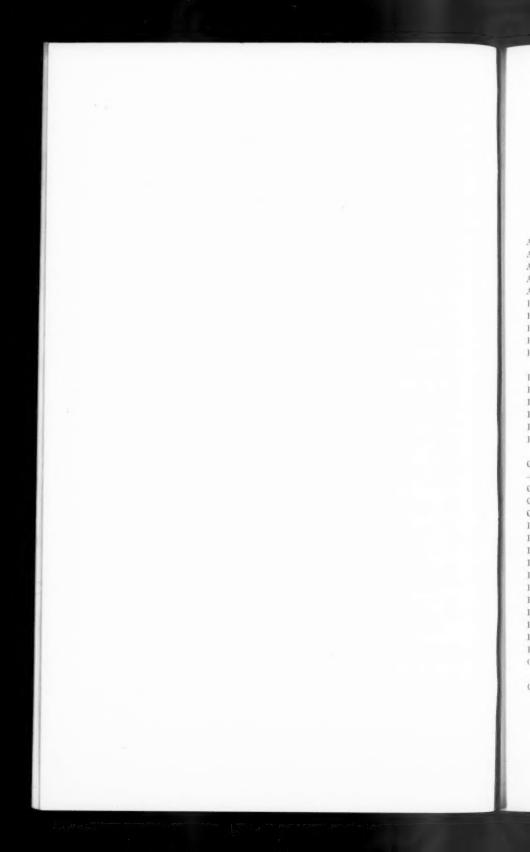
4) In 51 Fällen wurde die Einwirkung eisgekühlter Milch sowie eisgekühlten Bariumbreies, die mit der Magensonde zugeführt wurden, auf das periphere Blutbild (in 5 der Fälle wurde zur Kontrolle + 37 C° warmer Bariumbrei zugeführt) untersucht. Auch in diesen Versuchen wurde festgestellt, dass der Erythrozytenwert und Hämoglobingehalt durchgehend absinken. Schon 15 Minuten nach Zuführung der eisgekühlten Milch war der Erythrozytenwert durchschnittlich um 8,5 % niedriger als vor dem Versuch. Das Minimum der Erythrozytenwerte wurde 45 Minuten—1 Stunde nach Darreichung der kalten Milch festgestellt. Ab 1 Stunde 30 Minuten nach Zuführung der Milch stiegen die Erythrozytenwerte an, hatten aber 3 Stunden 30 Minuten nach dem Versuch den Ausgangswert noch nicht

erreicht. Ähnlich waren die Veränderungen nach Zuführung eisgekühlten Bariumbreies; der warme dagegen verursachte ein Ansteigen der Erythrozytenwerte.

Die Veränderungen der Leukozytenwerte wiesen keine Regelmassigkeit auf; im grössten Teil der Fälle nahm ihr Wert ab. Die absolute Zahl der Segmentkernigen und Lymphozyten wies in zahlreicheren Fällen eine Abnahme auf.

Der kalte Bariumbrei verursachte keine verlangsamte Ventrikelentleerung, in einigen Fällen war sie sogar beschleunigt.

Weder vor noch nach dem Kältereiz waren Jugendformen der Leukozyten und Erythroblasten nachweisbar.



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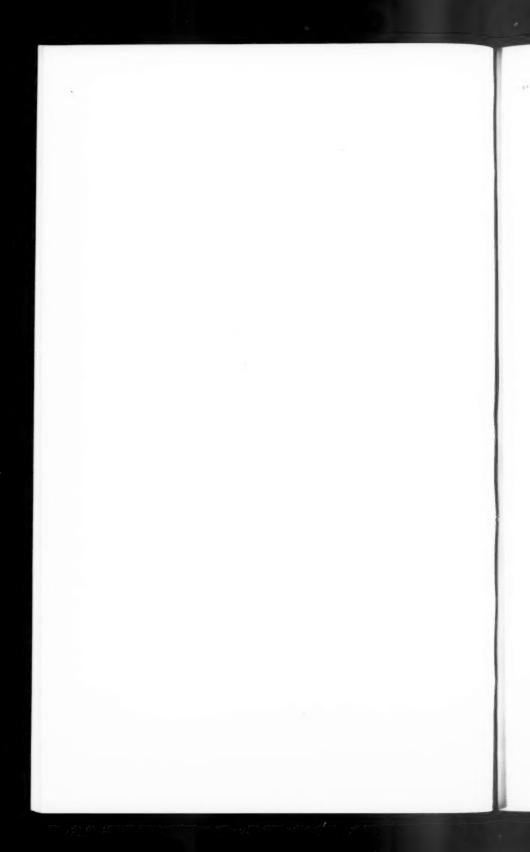
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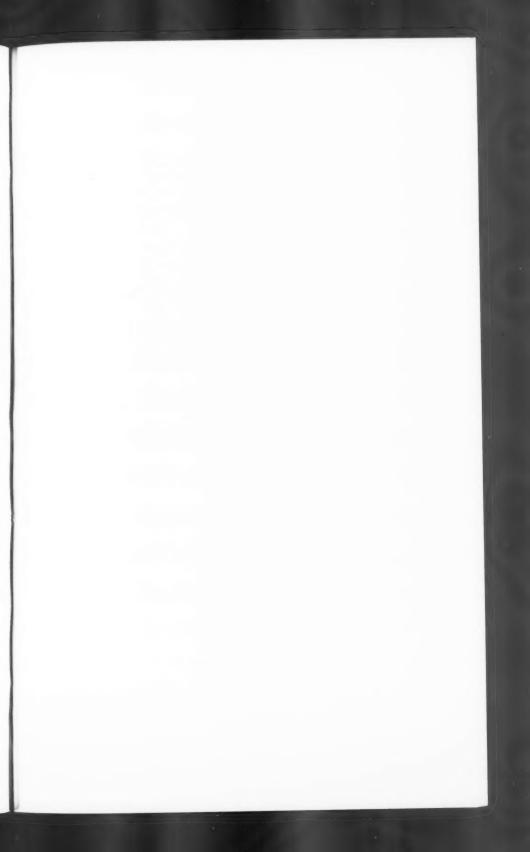
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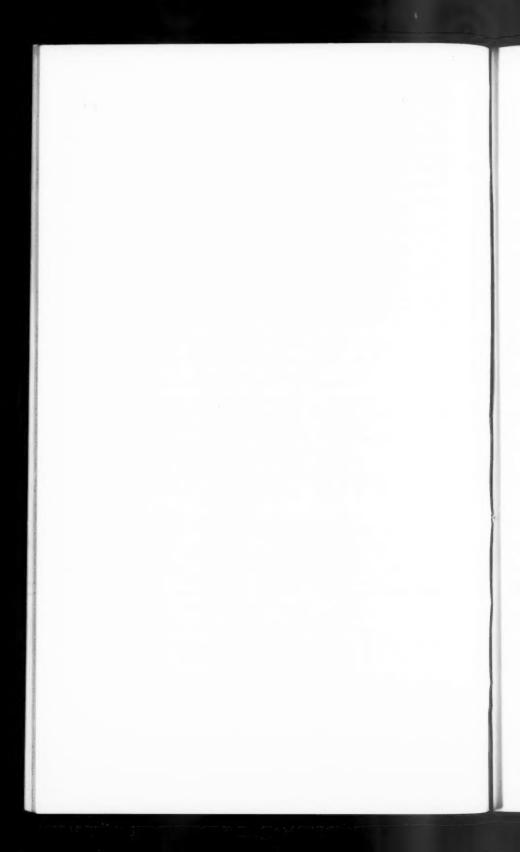
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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY, HELSINKI,
CHIEF: PROF. ARVO YLPPÖ, M.D., AND FROM THE MUNICIPAL EPIDEMIC
HOSPITAL OF HELSINKI, CHIEF: PROF. VILJO RANTASALO, M.D.

STUDIES ON THE CEREBROSPINAL FLUID IN PREMATURE INFANTS

BY

EINO OTILA

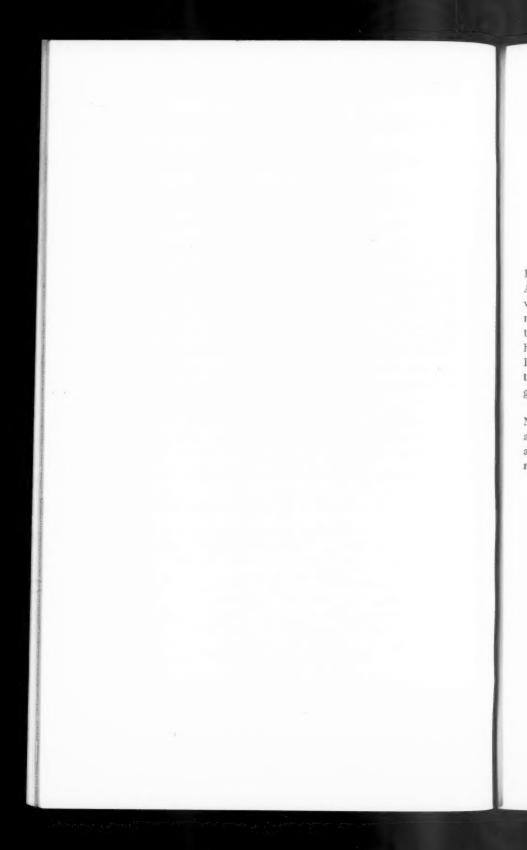
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HELSINKI 1948

HELSINKI 1948 MERCATORIN KIRJAPAINO

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PREFACE

In presenting this report of my studies on premature infants I wish in the first place to express my gratitude to Professor Arvo Ylppö, M.D., for suggesting to me the subject of the investigation and for providing me in the course of the work with much valuable advice and helpful comment greatly facilitating the investigation. He also has made available to me cases in the hospital headed by him. My thanks are also due to Professor Viljo Rantasalo, M.D., who has kindly allowed me to conduct examinations in the hospital of which he is the head and who has shown great interest in my work.

Further I am indebted to Miss Helvi Pölönen, Laboratory Nurse, for making the sugar determinations included in this work and assisting me in carrying out the tryptophan and mastic reactions. I also thank Miss Elvi Kaukokallio for translating the report of my investigation into English.

Helsinki, April 1948.

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I. Introduction

QUINCKE was the first to demonstrate in 1891 the performance of a lumbar puncture upon a living human subject for the withdrawal of cerebrospinal fluid. A period of »incubation» then passed before more intensive study was focused upon this fluid. Fears were entertained of possible undesirable effects upon the person punctured, and such consequences were also reported to have occurred. Clinicians at first were also doubtful of the diagnostic and therapeutic significance of the lumbar puncture. Little by little, however, the technique of lumbar puncture improved, serious consequences to the subject became rare, and unpleasant sensations were less intense and less frequent. The ground was thus soon prepared for a more comprehensive and systematic study of the cerebrospinal fluid. Greater weight was at first placed upon the therapeutic value of the lumbar puncture, this aspect also being stressed by Quincke.

The methods of investigation were brought a further step forward by studies on the cerebrospinal fluid in syphilogenic pathological conditions of the central nervous system. These studies also brought the research work carried out in this field to the knowledge of wide circles, and they were followed by further development and improvement of the examination methods through the work of Siemerling (1904), Nonne (1908), Pandy (1910) and Kafka (1910, 1912, 1921), to mention but a few of the numerous investigators. Problems of also a purely theoretic nature soon gained prominence, including a large number of interesting points relating to clinical thought and practice.

Cerebrospinal fluid research, which for some length of time had been a matter of interest chiefly for the neurologist and the psychiatrist, now entered almost all fields of medical science. As a result, an extensive literature has accumulated on studies of the cerebrospinal fluid in both healthy and diseased conditions of the human organism, and investigations have been directed upon the most varied properties of the fluid.

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A great deal of study has been accorded the cerebrospinal duid in childhood. In 1931 Samson published a fairly comprehensive work entitled »Die Liquordiagnostik im Kindesalter», which contains in addition to the results of his own investigations a survey of the results obtained and methods employed by several other workers. Samson places emphasis upon the importance of a knowledge of the normal values and characteristics of the cerebrospinal fluid in order to enable differentiation, in diagnostication, of physiological and pathological conditions. He also states that it has been revealed with increasing clarity that childhood is not a uniform entity but should be divided into several subdivisions and that study must therefore be made of the normal cerebrospinal values in each separate subgroup.

The work of Samson as well as that of the other investigators mentioned describe a fairly active and varied study of the cerebrospinal fluid in the later periods of childhood. The fluid of the full weight (full term) newborn infant has also interested numerous workers, but the majority of them have been primarily concerned with the presence or absence of blood in the fluid, attempting to diagnose from this finding the possible occurrence of cerebral hemorrhage at delivery. Simultaneous determination of the number of white blood cells present in the fluid has been made by some workers. A very limited number only have systematically observed the properties of the fluid over a greater length of time in childhood. In fact, Samson is the only investigator who has systematically studied from several aspects the properties of the cerebrospinal fluid with full weight infants during the first three months of life as well as later.

The properties of the cerebrospinal fluid in premature infants have been accorded very little attention. It is true that there are

premature infants in the materials of some of the investigators, but systematic studies on a purely premature material and upon several properties of the fluid have been made by Samson alone (193!). It is to be regretted, however, that he does not state the size of the material studied by him.

Someon found in his investigations that the properties of the cerebrospinal fluid of the premature newborn differ to some degree from those of the full weight newborn and moderately from those of the older children and adults. He found that the most significant deviations in the fluid of premature infants in their first months of life are a greater number of cells and a higher concentration of proteins than usually are encountered. He regards an increase in the meningeal permeability as responsible for these phenomena and the latter therefore as a fully normal physiological condition. This concept is quite contradictory to that of Waitz (1928), who, encountering in the cerebrospinal fluid of premature newborn infants cell and protein concentrations which were greatly in excess of the usual values, regards them as pathological and due to meningitic conditions.

In view, therefore, of the limited study made in the past of the cerebrospinal fluid of the premature infant, and in consideration also of the fact that the extensive pathoanatomical research work carried out by Ylppö (1919) has demonstrated the very common incidence of cerebral hemorrhages sub partu in the premature newborn and the possible consequences of such hemorrhages upon the future mental and physical development of the child (LITTLE 1862, YLPPÖ 1919, SCHWARTZ 1927, DOLLINGER 1927, RYDBERG 1928, Brander 1936) it could be foreseen that a study of the cerebrospinal fluid of premature infants would offer a field of work of considerable interest. Upon the recommendation of Professor Ylppö I therefore undertook in 1938 to examine a large number of specimens of cerebrospinal fluid collected from premature infants and to compare the properties of these fluids with the characteristics of those withdrawn from full weight infants.

When my investigations had yielded results which were analogous to those of Samson in pointing to an increased meningeal

permeability in the premature infant, I was also assigned by Professor Ylppö the work of carrying out experimental studies on meningeal permeability by performing lumbar punctures on premature infants following the intramuscular injection of a stain, for the purpose of determining the rapidity and amount of diffusion of the stain into the cerebrospinal fluid.

World War II having intervened, the completion of $my\ w_{0T}k$ was delayed for several years.

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II. The Problems to be Solved

In conducting these investigations I have directed my principal attention upon such properties of the cerebrospinal fluid of the premature infant as are the chief subjects of interest in clinical work and research. Accordingly the questions which I have sought to solve in the present studies are the following:

- 1. A. How successful is the withdrawal of cerebrospinal fluid from the premature infant?
- B. How much cerebrospinal fluid may be removed from the premature infant without adverse effect upon the child?
- C. What is the amount of cerebrospinal fluid present in the central nervous system of the premature infant?
- 2. A. What is the effect of a possible cerebral hemorrhage occurring sub partu upon the appearance of the cerebrospinal fluid of the premature infant?
- B. Does neonatal icterus of the premature infant have any effect upon the color of the cerebrospinal fluid?
- C. Can the appearance of the cerebrospinal fluid and the results of investigations related thereto be employed as indication of the presence or absence of cerebral hemorrhage occurring sub partu?
- 3. A. What is the cell count and the amount of protein present in the cerebrospinal fluid of the premature infant in comparison with those of the full weight newborn and the normal adult?
- B. Has the weight at birth and age of the premature infant any correlation with possible variances in the cell count and the protein content?

- C. What is the probable causative factor of such variances, if found?
- 4. Are any qualitative deviations from the normal recognizable in the proteins present in the cerebrospinal fluid of the premature infant?
- 5. What is the sugar content of the cerebrospinal fluid of the premature infant and what is its relation to the sugar content of the blood?
- 6. Is a foreign substance, such as for instance uranin, when injected intramuscularly into the premature infant, recognizable in the cerebrospinal fluid, and can inferences be made from this phenomenon regarding the permeability of the hemato-encephalic barrier of the premature infant?

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III. Material

In this work the term premature infant is used to designate a child whose weight at birth is $\leq 2,500$ g. irrespective of the duration of the pregnancy (Ylppö 1919).

My material consists of 100 »healthy premature infants», upon whom I performed a total of 200 punctures. By a healthy premature infant I herein denote a premature infant in whom no malformations or signs of infectious diseases are found.

According to the weight at birth the cases are divided into the following three groups:

The mean weight at birth of all the premature infants in my material is 1,795 g., being in the different groups as follows:

There are 48 male and 52 female infants in the series. Of the 100 children examined, 54 were from the Children's Clinic of the University of Helsinki and 45 from the children's ward of the Municipal Epidemic Hospital of Helsinki; one child was punctured at the consulting station of the Municipal Epidemic Hospital. Sixty-five of the 200 punctures were made at the Pediatric Clinic of the University and 135 at the Epidemic Hospital. At times when contagious diseases are not prevalent, the latter hospital devotes part of its space to aseptic children's wards, among others for the care of premature infants.

A single puncture was performed on 67 premature infants The remaining 33 children were punctured more than once and are classified as follows according to the number of punctures:

TABLE 1
Cases Punctured More than Once

No. of Punctures	No. of Case	
2	10	
3	5	
4	5	
5	6	
6	3	
7	2	
8	2	
Total	33	

At each puncture I observed the appearance of the cerebrospinal fluid, performed Pandy's reaction, and made the leukocyte and erythrocyte counts. These observations and tests were carried out by myself in every case. Quantitative determination was made of the amount of proteins in the cerebrospinal fluid in the case of 93 infants, a total of 191 fluid specimens being tested, equal to 95.5 per cent of the total number of punctures.

The sugar content of the cerebrospinal fluid was determined in 51 cases and a comparative determination was simultaneously made from the blood in 26 cases.

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I carried out the tryptophan reaction in the case of 37 premature infants and from 57 specimens of cerebrospinal fluid. The mastic reaction was carried out on 21 infants and from 22 specimens, and the Wassermann reaction from the fluid of 80 infants. As the WR was negative in all of the 80 cases I deemed it sufficient, in order to save the child's cerebrospinal fluid specimen for other tests, that a negative Wassermann reaction was obtained from the mother's blood in the remaining 20 cases.

The age of the child at the time of the first puncture varies greatly, ranging from three hours to over one year.

In the cases of more than one puncture on the same child, an interval of at least two weeks was allowed to elapse between the punctures except in the following few cases, i.e., 13 days in three cases, 12 days in one case, and 10 days in three cases. Five premature newborn infants were punctured within the first 24 hours of life. The total number of punctures is classified according to the different sage groups of the children as follows:

TABLE 2

Total Number of Cases Punctured, Glassified according to Age

Age in Months	No. of Puncture		
0-1/4	21		
1/41/2	15		
12-1	30		
1-112	31		
112-2	25		
2 - 3	39		
34	10		
46	13		
6 - 12	11		
over 12	5		
Total	200		

The lowest birth weight in my material was 900 g. This child was punctured 23 hours after birth, the weight then being 890 g. (case No. 5). The weight of 2,500 g. regarded as maximum for prematurity was registered by two newborn in my material. The lowest weight at the time of puncture was 730 g., having been 1,160 g. at birth, and the puncture was performed on the eighteenth day (case No. 38). The highest weight at puncture was 9,980 g., this child also being the oldest to be punctured (1 year 4 months).

The series used for my investigations on meningeal permeability carried out with usanin comprises 11 premature infants, on whom a total of 37 successful punctures were performed. The term »successful puncture» designates herein the presence of no blood in the spinal fluid. The control series for the uranin test also comprises 11 full weight infants, on whom I made 38 succes ful punctures.

IV. Methods of Investigation

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With a single exception I employed in all the cases the lumbar puncture for the withdrawal of specimens of cerebrospinal fluid from the infants. In the one case in which a cisternal, or occipital, puncture was used, the weight of the child at birth was 900 g, and the puncture was made shortly after birth. This occurred in the initial stage of my work, when I entertained a fear of producing by the lumbar puncture an artefact hemorrhage in so small a subject.

I have only made macroscopic estimation of the color of the fluid by viewing it in the test tube against a white background.

For the cell count the Fuchs-Rosenthal (1904) counting cell method was exclusively employed, as I consider it the best and most accurate procedure now in use. In this method the cell count is usually expressed by the number of cells counted in the chamber followed by the divisor 3, and the cell count per cubic millimeter is obtained by dividing the number of cells stated by 3. For the sake of clarity I have in describing the results of my present investigations already carried out this calculation.

A leukocyte pipet with the graduation lines 1 and 11 is widely used to obtain the correct proportions in mixing cerebrospinal fluid and staining fluid. However, contrary to what the procedure is with the blood specimen in making the leukocyte count, cerebrospinal fluid is not drawn into the pipet up to the line 1 and staining fluid up to 11 but the procedure is reversed, staining fluid first being drawn to 1 and then cerebrospinal fluid to 11. There thus will be 10 parts of cerebrospinal fluid in the total of 11 parts. However, I abandoned this procedure after the initial phases of my work because of the drawback that the staining fluid which remained in the point of the pipet rendered unfit for other tests the remainder of the portion of cerebrospinal fluid — even if small — separated for the cell count. Every drop of fluid from the tiny premature infant is invaluable, as one is reluctant to withdraw very much and there are numerous tests

to be carried out. To be economical with the specimens I adopted the following method suggested by Kafka (1910), which is both simple and convenient. Ten drops of cerebrospinal fluid and, after cleansing of the pipet, one drop of staining fluid are deposited into a narrow test tube from a small capillary pipet. The ratio of 10:11 identical with that used in the procedure described above is thus obtained. The major advantage of this method is that it requires very small amounts of cerebrospinal fluid. Furthermore the addition of the stain is very simple and rapid and the fluid thus is soon ready for the cell count.

To stain the cerebrospinal fluid cells most investigators have employed methylene blue in a 3 to 10 per cent solution of acetic acid. It is, however, the opinion of Samson (1931) that methylene blue does not bring out the nuclear forms with sufficient clarity and that frequently the red blood cells also take a strong stain, rendering differentiation from the white blood cells difficult. He therefore adopted the use of the following solution:

Acidum	aceticum glaciale	30.0
Acidum	carbolicum liquefactum	2.0
Fuchsin	in alcoholic solution (1:10)	2.0
Aqua de	estillata ad	100.0

With the exception of a few stainings with methylene blue I have used Samson's solution, which I found to be well suited for the purpose. The stability of the solution is excellent and filtration is unnecessary prior to use. The composition of the solution is such in nature that the stain penetrates the cells rather slowly and therefore about thirty minutes are required for the action of the stain before the cell count is made. The stained cells are then very distinct and a few hours later they are even more clearly defined. Accordingly this method enables easy differentiation of the cellular forms directly in the counting cell.

I carried out Pandy's reaction in the modified form developed by ZALOZIECKI (1913), which probably is the method most widely in use at the present time. The procedure is the following: A small amount of carbolic acid reagent is poured on a watch crystal, a drop of cerebrospinal fluid is added, and immediate estimation is made of possible opalescence, faint turbidity, distinct turbidity, or actual precipitation in the fluid. It is advisable to place the watch crystal against a black background and to throw on a light from the side.

A fully clear reagent stored in a dark container is indispensable. Contact with air will produce a slight turbidity on the surface of the reagent and the process must therefore be carried out immediately after the reagent is poured on the watch crystal. Differentiation between a negative and a positive reaction is sometimes difficult, as the drop of cerebrospinal fluid may only produce a faint opalescence. A definitely negative reaction is conclusive evidence of a normal protein content. The symbols used in the

present investigation in describing the results of Pandy's test are the following: faint opalescence \pm , turbidity +, very pronounced turbidity ++, and precipitation +++.

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The quantitative protein determinations for this work were made at the State Serum Laboratory in Helsinki. The procedure employed in the laboratory is the colorimetric method developed by Leenla (1932) and based upon the xanthoproteic reaction. The total nitrogen content (N reading) is obtained by means of the Leikola-Noponen universal comparator and the quantitative protein content by multiplying this reading by the Kjeldahl index figure 0.0625. The Wassermann reactions also were carried out at the State Serum Laboratory.

The CRECELIUS-SEIFERT method (1928) was employed in the tests for sugar. I am fully aware that the values obtained by this method are not as dependable as those given by the Hagedorn-Jensen method, but practical and economical reasons dictated my choice, as no other method was available at the hospital where these tests were conducted.

I carried out the tryptophan test by the Furth-Nobel (1920) in thod, adding 15 cc. of concentrated hydrochloric acid (specific weight 1.190) to 2 to 3 cc. of cerebrospinal fluid and then adding to this 3 drops of 2 per cent formaldehyde. The mixture is thoroughly shaken and five minutes later it is overlaid with 2 cc. of a 0.06 per cent solution of sodium nitrate. If tryptophan is present in the cerebrospinal fluid a violet ring is formed in about three minutes at the level where the two fluids meet. In the absence of tryptophan a gray or yellowish turbidity is frequently recognizable at the junction, but it is readily distinguished from a positive reaction, in which a yellowish ring immediately forms and soon turns a violet color.

For the mastic reaction I employed the Sahlgren method (1922), using a series of six tubes. The readings are indicated by figures as follows:

0 = opalescence

1 = slight turbidity

2 = pronounced turbidity or slight precipitation

3 = pronounced precipitation

4 = complete precipitation (fluid is clear).

For determination of meningeal permeability I employed the so-called uranin method. Intramuscular injections of 0.02 g. of uranin (fluorescein sodium) to the kilogram of body weight were administered in the form of a 20 per cent solution. In the first case examined the injection contained 0.03 g. of uranin per kilogram of body weight, but this dosage was immediately reduced to 0.02 g. in view of the powerful staining observed in the subject and the permeation of the staining medium into the cerebrospinal fluid in so large an amount as to interfere with the precision of the test.

In the early part of my series I performed the lumbar puncture also in the case of premature infants exactly two and one-half hours after the intramuscular injection of uranin, in conformity with the procedure described in the most recent literature. However, in the case of premature infants and also of full weight infants in their first months of life in the control series I soon adopted a schedule calling for initial puncture already one-half or one hour after the uranin injection and further punctures at intervals of one-half or one hour until two and one-half hours and in some cases even a longer time had passed from the administering of the injection.

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For the uranin test about 2 to 3 cc. of cerebrospinal fluid were generally drawn from the subject; Pandy's reaction and the cell count were also taken from this specimen. The uranin content was determined by means of a fluoroscope of simple construction, easily set up by anyone. The inside walls of a small wooden box are painted black and two holes are drilled side by side on the top cover to accommodate two test tubes about 1/2 cm. in diameter, which protrude approximately 2 cm. above the top, cover. The test tubes used by me were about 10 to 12 cm. in length. A transverse slit is made in the front wall of the box, fairly low down. When a light in a cylindrical housing is placed directly upon the box, even a very faint fluorescence is clearly discernible when the test tubes are viewed through the slit. One cubic centimeter of cerebrospinal fluid is sufficient for estimation of the fluorescence. Distilled water was used in the other test tube as control. If any degree of fluorescence was observed in the undiluted specimen of cerebrospinal fluid, dilution was made with distilled water, using fluid and water in equal parts. Dilution was continued until no fluorescence was visible. The greater the number of dilutions necessary the higher the uranin content. In performing this test extreme care should be taken that no blood is present in the cerebrospinal fluid to be examined. Should blood be present, it may have entered the fluid from a blood vessel injured at puncture and thus have conveyed uranin directly from the blood into the cerebrospinal fluid without its passing through the barrier of the central nervous and blood circulation systems. It is difficult, though not always impossible, to make a number of »bloodless» lumbar punctures at short intervals upon subjects as small as a premature infant.

The methods of investigation employed in the present work have been described above in great detail, for in the case of cerebrospinal fluid examinations, in which the methods used still greatly lack uniformity, it is important to know what procedures have been followed in order to be able to control, compare and correctly evaluate the results of my investigations.

V. Success of the Lumbar Puncture and Amount of Cerebrospinal Fluid in the Premature Infant

Speaking in general of the different methods of puncture used for the withdrawal of cerebrospinal fluid, Samson (1931) states: »Erfolglose Punktionen kommen bei allen Punktionsarten vor. ohne dass man immer sofort den Grund finden kann. In einzelnen Fällen ist wirklich keine Flüssigkeit vorhanden. Beim Neugeborenen ist dies manchmal der Fall. Gründe für vergebliche Punktionen können sonst in der Technik zu suchen sein, zu tiefer oder zu geringer Einstich, Unmöglichkeit den Lumbalkanal bei Verbiegungen zu treffen.» In view of the very few reports on lumbar punctures on premature infants published in the literature I shall here briefly review also the results obtained with full weight infants. SHARPE and McLaire (1925) performed punctures on 400 newborn infants but were unable to withdraw spinal fluid in 6 per cent of the cases. Levinson, Greengard and Lifvendahl (1926) punctured 100 full weight infants, of whom 24 had a lumbar puncture only, 64 a cervical puncture only, and 12 both punctures. Accordingly the total number of punctures made was 112. In five of the cases, i.e. in three lumbar and two cervical punctures, these investigators obtained no fluid. They also report greatly varying lengths of time - from a few seconds to as much as two and even three minutes - for the appearance of the first drop of fluid in the base of the needle. The rapidity of flow also varied from one drop per second to one drop in 35 seconds. Samson (1931) punctured 40 newborn infants, from whom no fluid was obtained in eight cases (20 per cent). Among the latter, however, are included

two cases in which very profuse hemorrhage occurred immediately upon insertion of the needle, necessitating interruption of the procedure. If these two doubtful cases are disregarded, the failures total 15 per cent of all the cases punctured by him.

Waitz (1928) describes punctures on 300 newborn infants soon after birth. He could collect no cerebrospinal fluid in 83 per cent of the cases, very little in 7 per cent (in the majority of cases a few drops only), and an abundance of fluid in 10 per cent of the punctures. He also states that in those cases which yielded cerebrospinal fluid, none was obtainable three to five days later in two cases, six to eight days later in two cases, and nine to eleven days later in three cases.

Framm (1924) performed punctures on premature infants, making a total of 18 punctures on 11 children. No mention is made of failures. Samson (1931) reports equal success in punctures on premature as on full weight infants, i.e. failure in about 15 per cent of the cases. The size of the material is not indicated by him.

Personal Investigations

In undertaking to perform lumbar punctures on premature infants I was prepared for failure in many cases, as the literature reports numerous unsuccessful punctures on full weight infants. This fear, however, proved unfounded, as in my own material I failed to obtain fluid from two punctures only and even in these cases a fair amount could be drawn on the following day. In a few cases, it is true, the first few drops of the fluid were slightly blood-tinged.

The success of my lumbar punctures is probably accountable in part to the technique of puncture which I was in a position to develop particularly during my service as assistant physician at the Helsinki Municipal Epidemic Hospital, where I was called upon to perform a great number of lumbar punctures, especially on poliomyelitis and meningitis patients.

With adults and older children the site chosen for the lumbar puncture is usually between the third and fourth lumbar vertebrae, which is on an approximate level with a straight line drawn between the cristae iliacae. Corroborating the findings of Levinson (1928) and Samson (1931) it has been my experience that with young infants and in general with children under one year of age it is well to make the lumbar puncture at a slightly higher level, i.e. between the first and second, or between the second and third lumbar vertebrae, for the lumbar canal of these children does not extend as far as that of older children. For this reason it is advisable to localize the punctures still higher on the premature infant, preferably between the first and second lumbar vertebrae, i.e. about two centimeters above the connecting line of the cristae iliacae, so as to best avoid injury to the blood vessels which are very abundant at the termination of the lumbar canal.

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It is my experience that the best results in lumbar punctures on premature infants are achieved if the child is held by the nurse in the sitting posture, as also recommended by Glaser (1930), with its back fairly well curved outward. The child must be held fixed to prevent it from twisting about, and the head must face straight ahead and bend somewhat forward. The puncture needle is best inserted exactly in the median line. I used needles 4.0 cm. in length and 1.2 mm. in diameter, fitted with a mandrin. The longer the needle the harder its accurate control. The point of the needle must of course be as sharp but at the same time as short as possible in order not to injure, when in the lumbar canal, the blood vessel plexus in the ventral wall.

Before undertaking the work itself I tested out the different puncturing methods and instruments recommended by the various investigators. As was already mentioned above, a long needle was at once found inconvenient and unsuitable, as also were injection needles of various sizes without a mandrin. I also attempted punctures with the child lying on its side. This posture I found helpful with somewhat older infants, as even relatively strong children could then be induced to remain in a fixed postion fairly well. However, with delicate premature infants the locating of the spinal canal involves very much greater difficulty in a lying than in a sitting posture. Furthermore, the cerebrospinal fluid emits in the latter case with a greater pressure and therefore at a more rapid rate than when the child is lying down. It is important to with-

draw from the very small premature infant a sufficient quantity of fluid with a minimum of delay so as to avoid exposing it for very long and thus subjecting it to an excessive loss of heat.

I did not consider it necessary to take pressure measurements of the cerebrospinal fluid in premature infants, as this procedure is complicated by very marked difficulties and as the possibility of errors in the evaluation of the readings is great. Correct values are of course unattainable when the child cries. Also, the prone position would be preferable if correct and accurate results are desired. Furthermore the aperture of the puncture needle may be partly covered by membranes, permitting but slow emission of the fluid. These are some of the reasons why I made no measurements of the cerebrospinal fluid pressure.

However, the pressure of the fluid generally is so great even in the smallest premature infant, at least when the child is held seated, that the fluid emits from the spinal canal at a moderately good rate. Many investigators have recommended the use of an aspirator when puncturing young infants; however, if the physician has developed a good technique this is quite unnecessary. Samson (1931) furthermore states that in most cases where suction is employed blood enters the fluid. If the dripping of the fluid is extremely slow it can be accelerated by compression of the jugular veins. However, I found this necessary in two or three instances only.

For disinfection of the skin preceding the puncture I used a 2 per cent solution of tincture of iodine, which did not irritate even the most delicate skin, as sometimes is the case with a 5 per cent solution. In any case it is advisable to wipe off the iodine with alcohol immediately after puncture. Anesthetization of the skin prior to puncture is in my opinion an entirely needless precaution in the case of premature infants.

The optimum depth of insertion of the lumbar puncture needle is subject to great variance even with premature children. This is readily comprehensible, for the layers to be penetrated, i.e. the skin, superficial fascia, fatty tissue, deep fascia, muscle, intervertebral foramen, ligamentum flavum of the dorsal wall of the spinal canal, dura mater, and arachnoid, each and all may vary in thickness. Samson (1931) is of the opinion that punctures on prema-

ture infants should be made to a depth of about 1.5 to 2.0 cm. I have sometimes been able to withdrawfluid from the very small premature infant at a depth of only 0.5 cm. In the first six months of life the depth of 2.5 cm. need hardly be exceeded, whereas in the following six months even the 3 cm. depth may sometimes be attained.

When a lumbar puncture upon a premature infant is being performed, the hand should be very sensitive and the needle introduced with the utmost care. In most cases it will then he possible to feel when the needle penetrates the dorsal ligament and the membranes of the canal. It is preferable to remove the mandrin too often rather than too seldom, for even the slightest contact of the point of the needle with the ventral wall of the spinal canal, where there is an abundance of blood vessels, frequently produces hemorrhage greatly interfering with the investigation. A procedure to be recommended in the case of very slight or total absence of flow of cerebrospinal fluid, when the needle already is believed to have properly entered the canal, is to rotate the needle very slowly around its longitudinal axis. This slow rotatory movement is greatly to be preferred to a back and forth movement of the needle. The point of the needle is sometimes in a poor position in relation to the membranes and this is readily improved by the slight rotation described above. After completed puncture and removal of the needle, massage with a light circular motion over the site of the puncture is beneficial in order to promote the approximation of the layers of tissue and thus prevent further escape of cerebrospinal fluid.

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In the punctures which I performed, one or two seconds only or a few seconds at the most were required from the moment the point of the needle properly entered the spinal canal to the appearance of the first drop of fluid in the base of the needle. Except for a very few cases, the fluid issued in rapidly following drops or actually in a spurt. If the child cries or greatly strains its muscles during the puncture, the fluid frequently spurts forth, but also an opposite effect can be noted. In the few cases in which withdrawal of fluid was slow at first (one drop in about five seconds) a more rapid rate was induced by a slight rotation of the needle around its longitudinal axis.

At the outset of my work I did not dare, except in a few cases, to remove more than about 3 cc. of fluid at a time from any premature child even if the weight already had increased appreciably in comparison to the birth weight. I then gradually passed over to a schedule according to which about 3 cc., as before, were drawn from infants in the first group (birth weight 1,500 g. or less) and about 5 cc. from all the other premature children. As I gained courage I frequently drained at each puncture about 5 cc. even from the infants in the first group and sometimes as much as 8 cc. from the others. I noted no untoward effects from the puncture even in the smallest premature child nor any disturbance in the normal increase of weight. Only once it did occur during puncture that the child became pale and slightly limp. This happened in the case of the fifth puncture on a child whose weight at the time was already 2,850 g. (case No. 16). The child recovered rapidly and regained its former state in one or two minutes, no stimulant being required. The muscles of this child were relatively strongly developed and during the puncture it screamed and strained them hard, and a large amount of cerebrospinal fluid spurted out. Apparently the very sudden change in pressure produced this rapidly transient state. After withdrawal of a relatively large amount of fluid I frequently observed that the fontanel was slightly drawn in. This interstice forms in the infant an excellent »pressure regulator». The depression was no longer observable in most cases after one hour and in no cases was it seen after two hours from puncture.

In postmortal punctures on premature infants, made within one hour after death (outside of the material proper of this work), I allowed the total amount of cerebrospinal fluid obtainable to drain out. In this way I obtained from 6 to 10 cc. of fluid from premature infants of the first group and from 10 to 15 cc. from the larger premature infants.

On the basis of experience gained in connection with my own material I believe I am correct in stating that the reason for failure to obtain cerebrospinal fluid in punctures on premature infants or on newborn children in general is in the majority of cases to be found in the performance of the puncture itself, or more precisely

in the technique, provided the punctured child is a normally developed individual aside from its low weight. It is of course a different matter should pathologic changes such as a tumor, inflammatory stenosis, or other condition be present which wholly or even in part occludes the communicating passages of the central nervous system, or if the cerebrospinal fluid is so thick due to purulent meningitis or to coagulation of the blood that it cannot pass through the lumen of the needle. The concept that cerebrospinal fluid is not always present in the spinal canal of the normal premature or newborn infant certainly is an erroneous one.

I wish to emphasize the advantage of the sitting position of the child when punctures are being made on premature infants. Already in 1899 this posture was recommended for young children by Pfaundler. Further factors of importance to the success of lumbar punctures on premature infants are an appropriate and efficient instrument and the correct posture of the infant at the moment of drainage of the fluid.

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My investigations provide grounds for the opinion that the lumbar puncture is a successful and fully harmless procedure also when performed upon premature infants of even the smallest size, provided that care is taken to keep the loss of heat as low as possible. Reports in the literature of fatal accidents in connection with punctures generally reveal that sudden death has occurred only in the presence of cerebral tumor (particularly in the fourth ventricle) or of fairly large aneurysm in the brain (Führbringer 1896, Gumprecht 1900, Levinson 1928). These conditions, however, are very rare with the premature infant and need not be taken into consideration in actual practice.

Since it is probable that only slightly over one-half of the total amount of cerebrospinal fluid can be withdrawn from the premature infant by lumbar puncture, I am of the opinion, on the basis of my present studies, that the amount of cerebrospinal fluid contained in small premature infants is about 10 to 20 cc. and in larger premature infants about 20 to 30 cc. These values are analogous to the results of Ylppö's investigations (1919) and to the values ranging from 40 to 60 cc. recorded in the literature for full term infants (Kruse 1930, Samson 1931).

VI. Appearance of the Cerebrospinal Fluid of the Premature Infant and Effect of Possible Cerebral Hemorrhage at Delivery

In appearance the normal cerebrospinal fluid is clear like water, transparent and colorless. The cerebrospinal fluid of the child does not differ from this norm except in the case of the newborn infant.

Under pathological conditions the appearance of the fluid may undergo considerable change. One may encounter turbidities which may be produced, for instance, by an increased number of cells, by a rise in the fibrinogen content, or by the presence of bacteria. Relatively small amounts of red blood cells (300 cells per cmm.) also may produce slight turbidity without simultaneous change of color.

A yellow hue probably is the most common abnormal coloring. It may be a very faint yellowish tinge, but also bright yellow, brownish yellow, and even reddish yellow fluids may be encountered. In the presence of large amounts of pus and particularly in inflammatory conditions caused by pneumococci, greenish hues are frequently seen. Red and reddish discoloration is of course chiefly due to the presence of blood.

Most of the investigators who have carried out studies on the cerebrospinal fluid of the newborn have focused their attention principally upon the appearance of the fluid and particularly upon color and the possible presence of blood. Many workers have sought to determine from these factors the probable occurrence of

cerebral hemorrhage at parturition. Roberts (1925), whose material of 423 newborn negro infants includes 54 premature cases, obtained a yellow fluid in all of the 423 cases. In 60 cases, or in 14 per cent, blood was present; among these were 15 premature infants (25 per cent). He found that this color was caused by the presence of bilirubin in the cerebrospinal fluid. In a later study (1928) Roberts ascertained that in newborn infants the bilirubin content of the blood in relation to that of the cerebrospinal fluid generally is 100:1 in cases where cerebral hemorrhage is not involved, whereas in the latter case the ratio is 30:1.

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LIEBE (1940) also states that it is possible to determine the occurrence of cerebral hemorrhage sub partu by comparison of the bilirubin values of the blood and of the cerebrospinal fluid by means of the method used by him. His material consists of 177 infants, among them 106 premature cases. He states that the children had been hospitalized for various diseased conditions, such as enteritis, pneumonia, malformation, and cerebral meningitis. It was a further objective of Liebe's investigation to indicate that cerebral hemorrhages are not more common with premature infants than with full weight newborn. This subject will be reverted to later in the present work.

Sharpe and McLaire (1925) performed punctures on 400 newborn infants. Blood-tinged fluid was obtained in 45 cases, or in 9 per cent of the punctures. In the majority of cases the fluid was yellow, this condition being attributed by these investigators to cerebral hemorrhage. The material of Garrahan (1928) comprises 177 specimens of cerebrospinal fluid, 20 of which were colorless and the remainder yellow. He found the yellow coloring to be due in most cases to the presence of bilirubin. Ullrich (1925) performed punctures on nearly 100 newborn infants in whom, on the basis of clinical symptoms, he suspected cerebral hemorrhage. The fluid was blood-tinged in 15 per cent of the cases.

Levinson, Greengaard and Lifvendahl (1926) found among 112 cerebrospinal fluid specimens 24 blood-tinged, 4 very bloody, and 12 colorless specimens, the remaining 72 being yellow or yellowish. No bilirubin could be established by these workers in the fluids with a yellow or yellowish coloring, and they regarded this

color as due to uric acid. Tests for blood also gave negative reactions in all the cases of yellow fluid.

WAITZ (1928) describes the appearance of cerebrospinal fluid specimens withdrawn by him from 30 infants immediately post partum. These fluids were colorless in 41 per cent, yellow in 8 per cent, reddish in 41 per cent, and red in 10 per cent. There thus were distinctly blood-tinged fluids, microscopically established, in 51 per cent of the cases. On the following days the colorless fluids retained their clarity whereas the originally blood-tinged fluids turned yellow or yellowish. The yellow tinge disappeared from all fluids in about one week.

Samson (1930) consistently found a yellow coloring in the cerebrospinal fluid of full weight infants during the first eight days of life. The intensity of the color varied greatly, ranging from a scarcely discernible tinge to a bright yellow. The fluids which were stained a very strong yellow always gave a positive bilirubin reaction, even if it often was weaker than would have been presumed from the intensity of the color. For this reason Samson regards as probable that in addition to bilirubin some other substance is also present and enhances the intensity of the huc.

Regarding his investigations on this problem in the premature infant Samson writes: »Der Liquor der frühgeborenen Kinder ist weit stärker und weit länger gelb gefärbt als der der ausgetragenen Kinder. Während man nach den ersten 8 Tagen nur in Ausnahmefällen beim ausgetragenen Kinde noch einen gelben Liquor begegnet, ist dies bei den Frühgeburten bis zum Ende der zweiten Woche die Regel. Darüber hinaus wird dieser Befund seltener und ist nach der 4. Woche von uns nicht mehr erhoben worden.»

Framm (1924) found in 11 premature cases one colorless fluid, whereas all the other were stained yellow. In six of these cases the fluid furthermore was blood-tinged. It is to be regretted that Framm does not report the age of the infants at the time of puncture. The presence of bilirubin was established in one case, and in another a faint yellow tinge was still present five weeks after the first puncture.

GLASER (1930) performed punctures on 170 premature infants and found a yellow tinge in the fluid of a child 52 days old. The

youngest premature infant whose fluid no longer had yellow coloring was aged 35 days.

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YLPPÖ (1919) states that when the cranium of a premature infant dying in the first postpartum days is opened, there emits in the majority of cases, particularly in those of premature infants with a birth weight of 1,500 g. or less, a large amount of fluid which in many cases is somewhat hemorrhagic, especially during the first three to five days of life. Later a more yellowish fluid is obtained. Ylppö was also able to establish the presence of bilirubin crystals in a specimen taken from the pia mater.

Personal Investigations

In my own cases I obtained from newborn premature infants (first fourteen days of life) specimens of cerebrospinal fluid which in two out of the 36 punctures made were slightly turbid, whereas in the remaining 34 cases they were clear. In both of the exceptional cases (No. 5 and 25), microscopic examination revealed as the cause of turbidity a small amount of red blood cells (approximately 860 and 460 cells per cmm. respectively), which however did not produce a distinct reddish stain. I am unable to indicate whether the blood found in the fluid in these two cases originated from a hemorrhage occurring at delivery or from a blood vessel injured at puncture. Probably this small number of blood-tinged fluids in my series does not indicate the correct incidence of effusion of blood into the cerebrospinal fluid in premature infants. Had my punctures been performed on maternity hospital cases the percentage of hemorrhages would probably have been higher. My present cases emanate from the ward in pediatric hospitals to which premature infants are transferred for care from maternity hospitals, and therefore most of the cases of severe cerebral hemorrhage are absent for the simple reason that these cases already had proved fatal at the place of birth.

It was not a specific purpose of my investigations to determine from the properties of the cerebrospinal fluid the possible presence of cerebral hemorrhages at birth. The number of neonatal punctures performed by me (36) is entirely too small and the composition of the material also in other respects unsuitable for such evaluation, for in general I was undesirous, among others for precautionary reasons, of performing punctures on premature infants in an asphyctic or otherwise very weak condition and of possibly so contributing to the fatality of the case. Another reason for my avoidance of punctures on such premature infants was a fear of bringing the punctures into bad repute by possible occurrence of death soon after the procedure.

The specimens of cerebrospinal fluid were not blood-tinged in a single one of the 134 punctures performed after the first 14 days of life. True, the first few drops were blood-tinged in a few cases, but the remainder of the fluid was fully clear. It therefore is plainly apparent that the blood merely entered the fluid from a blood vessel injured at puncture. The cerebrospinal fluid specimens contained blood in 2 per cent only of my material of 100 premature infants. If the total number of punctures performed is considered, blood-tinged fluid was drawn in 1 per cent only of the 200 punctures made.

Except for one case, I observed a yellow coloring in all the specimens withdrawn from the newborn infants in my material. The one colorless fluid was obtained from a child punctured at the age of ten days. The weight of this child was 2,090 g. at birth and 2,120 g. on the day of puncture (case No. 29). A yellow color was thus found in all the fluid specimens withdrawn during the first week of the infant's life. In the five cases puntured within the first 24 hours there were three yellow and two yellowish fluids.

I classify the specimens of cerebrospinal fluid collected from my material into four groups according to color as follows:

- I. Colorless fluids
- II. Fluids with a faint yellowish tinge
- III. Fluids with a yellowish, strong yellowish, and very strong yellowish coloration
- IV. Yellow fluids.

Table 3 shows the distribution according to color groups of the cerebrospinal fluid specimens collected from the premature infants under the age of two months.

TABLE 3

Color of the Cerebrospinal Fluid in Premature Infants

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A I Nf13	No. of	Color Groups				
Age in Months	Punctures	I	II	III	11	
0 1/4	21	0	1	9	1.1	
0 1/4 1/4 1/2	15	1	1 .	3	11	
1/23/4	14	5	2	-4	1	
3/41	16	10	2	3	1	
1-11/2	31	22	5	4	1	
1 ½2	25	23	2	- 0		
Total	122	61	13	23	2:	

It will be seen that in the second week of life a greater proportion of fluids (two-thirds) than at any other period within the first two months is entirely yellow. The same period was also found by Glaser (1930) to contain the highest amount of yellow fluids. This finding is in harmony with the observation made by Ylppö (1913) regarding a correlation between the severity of icterus and the bilirubin content of the blood in premature infants. Ylppö states: »Die Frühgeburten zeigen im allgemeinen einen sehr hohen Gallenfarbstoffgehalt in ihrem Blute. Der Anstieg dauert bei ihnen gewöhnlich 6—10 Tage und der Gallenfarbstoffgehalt hält sich bei ihnen wochenlang oberhalb der Grenze.»

In the third week of the infant's life my material shows a total number of colorless and faintly yellowish specimens which is equal to the total of strongly yellowish and yellow fluid specimens. Already in the fourth week of life over one-half of the fluid specimens are free from color. I have quite often noted a yellow tinge in specimens drawn as late as the first half of the second month; in the 31 cases which I punctured at this age, four yielded a strongly yellowish and five a faintly yellowish fluid. I also found the cerebrospinal fluid to be very yellow in children affected with icterus of pronounced severity. The same observation was made by Framm (1924). In my material the yellow stain persisted for the greatest length of time in the fluid of premature infants who were severely

icteric. So for instance cases No. 59 and 23 were particularly icteric, and the cerebrospinal fluid specimens obtained from them as late as on the 47th and 55th days respectively had a yellow stain.

I thus obtained in my investigations results which are divergent from those of Samson (1931), who reports that he has not encountered a single case of yellow cerebrospinal fluid after the fourth week of life of a premature child. Ylppö (1913) reports an increase in the amount of bile pigments in the blood of the fetus and thus demonstrates the intrauterine inception of neonatal icterus. In the light of the fact that the cerebrospinal fluid of a premature infant only a few hours old is stained yellow or yellowish, it is obvious that bile pigment is conveyed into the fluid already prior to birth. The pigment probably originates from the blood and disappears once more from the cerebrospinal fluid after the increased bilirubin content of the blood has declined to normal.

Anselmino and Hoffmann (1931) find that with icteric children the blood vessels of the skin permit a more than normal amount of pigment to permeate the vascular walls. These children probably possess also a higher degree of meningeal permeability than usually is the case.

Despite the fact that Levinson was unable to find bilirubin in yellow cerebrospinal fluids, all the other investigations described as well as the facts enumerated above unquestionably indicate that in the great majority of cases the yellow color observed in the cerebrospinal fluid of premature infants is, at least for the greater part, produced by bilirubin. However, the possible existence in some cases of also another contributory factor cannot be denied with certainty, and further investigation is required for the full clarification of this point.

Even if my own material does not specifically justify the drawing of conclusions on the correlation between the appearance of the cerebrospinal fluid and the possible occurrence of cerebral hemorrhages at delivery, I feel I may express the opinion that we tread on exceedingly uncertain ground if we use the appearance of the cerebrospinal fluid as a criterion of the presence or absence of cerebral hemorrhage. Some workers are too freely inclined to

diagnose the blood-tinged fluid withdrawn in the first neonatal days as originating from cerebral hemorrhage, whereas other investigators, e.g. Lippman (1916), Framm (1924), Levinson (1928), Roberts (1928) and Samson (1931), hold a reverse view, pointing out the ease with which an artefact effusion of blood into the cerebrospinal fluid may be occasioned even with the best technique of puncture. I support this view in full. Inferences made from blood-tinged fluids should not, in my opinion, be accepted without severe discrimination. By this I by no means wish to contend the common occurrence of cerebral hemorrhages with premature infants. On the contrary, I have at some autopsies ascertained the presence of cerebral hemorrhage although a preceding puncture had yielded a fully clear specimens of cerebrospinal fluid. Identical findings are reported also by Lippman and Levinson.

Attempts have been made by several workers to develop a method of investigation which would indicate whether a blood-tinged specimen is the result of cerebral hemorrhage (essential hemorrhage) or of hemorrhage induced by the puncture (accidental hemorrhage). Bernheim-Karrer (1918) states that in cases originating from cerebral hemorrhage he observed in the cerebrospinal fluid hematomacrophages, i.e. large leukocytes containing entire erythrocytes or their fragments. However, hematomacrophages are not always found; so for instance Samson (1931) states that he has rarely encountered them. Kafka, on the other hand, reports the finding of these cells also in accidental hemorrhages.

According to Schlack (1928) the yellow color produced in the cerebrospinal fluid by icterus becomes fainter when the specimen is kept in the test tube for a few days, whereas that due to decomposition of blood following essential hemorrhage does not fade. This investigator obtained a positive guaiac reaction from centrifuged cerebrospinal fluid in cases of essential hemorrhage but a negative reaction in accidental hemorrhage. However, to obviate errors, centrifugation is necessary within fifteen minutes from the withdrawal of the fluid by puncture.

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As stated above, certain investigators (LIPPMAN, LEVINSON, LIEBE) obtained from newborn infants immediately after birth cerebrospinal fluid specimens which contained no blood, yet at

subsequent autopsy found a cerebral hemorrhage. I have made similar findings in my own investigations. It seems improbable to me that in cases of this kind the cerebral hemorrhage can raise the bilirubin content of the cerebrospinal fluid in the same degree as in cases where the hemorrhage occasions diffusion of blood into the fluid. Where no cerebral hemorrhage is present it is apparent that the bilirubin encountered in the cerebrospinal fluid has entered from the blood by means of increased meningeal permeability. Numerous investigators (Feigel 1927, Leonow 1927, Essel-BRÜGGE 1929. SCHIPPERS and PETERS 1929. SCHAFERSTEIN 1929. Samson 1931) have found that the meningeal permeability is increased in children up to the end of their first year of life and particularly during the first six months. Most of these investigators have also found a marked increase in all conditions of cerebral meningitis and frequently also in other pathological conditions, for instance in pneumonia, enteritis and, in particular, intoxication. The study made by Liebe, referred to above, on comparative bilirubin determinations from the blood and the cerebrospinal fluid, on the evidence of which he claims that cerebral hemorrhages are as frequent with full weight infants as with the premature, contains according to his own statement a number of cases of these diseased conditions. In view of what has been said above, the results of Liebe's investigations in this respect probably cannot be regarded as definitely conclusive evidence.

A number of investigators, in their studies on the properties of the cerebrospinal fluid, speak of the presence or absence of clinical symptoms of cerebral hemorrhage, such as asphyxia, somnolence and irregularity of respiration, to mention only a few. In this connection I feel there is reason to point out that the various symptoms in the newborn regarded as probably arising from cerebral hemorrhage are extremely uncertain and in part indefinite, and they also may be due to numerous other causes, as for instance pulmonary atelectasy, aspiration of amniotic fluid, or pneumonia or other infectious diseases. Similarly a cerebral hemorrhage has been encountered at autopsy in infants manifesting no clinical symptoms. Inferences made from the clinical picture on the presence of cerebral hemorrhages are extremely unreliable, at least in

borderline cases, and are in my opinion permissible only as probabilities but not as conclusive evidence.

It was accordingly found in my studies that the specimens of cerebrospinal fluid of 100 premature infants contained 98 clear and 2 slightly turbid fluids. In the latter two cases microscopic examination revealed the presence of red blood cells as the cause of the turbidity.

With but one exception I found a yellow or at least a yellowish coloring in the cerebrospinal fluid of all the newborn premature infants in my material; the color was the most intense in the second week of life. The fluid remained yellow for a considerable length of time. Apparently the yellow stain was due to the presence of bilirubin, which is chiefly conveyed into the fluid from the blood by means of the probably greatly increased meningeal permeability of the premature infants. In some cases, however, a possible cerebral hemorrhage at delivery may have increased the bilirubin content of the cerebrospinal fluid.

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I reach the conclusion that in numerous cases it is possible to state on the basis of the appearance of the cerebrospinal fluid and by means of pertinent test methods that a cerebral hemorrhage may probably have occurred, but the procedures so far devised cannot in by far all the cases offer a basis for infallible conclusions on the presence or absence of cerebral hemorrhage.

VII. Cell Count in the Cerebrospinal Fluid of the Premature Infant

All investigators are not in full agreement regarding the cell content of the normal adult cerebrospinal fluid. Earlier in the past the presence of 0 to 5 cells per cubic millimeter was regarded as normal, 5 to 10 as marginal values, and values only over 10 as definitely pathological. Today the margin is drawn considerably lower. NEEL (1928) holds that the normal cerebrospinal fluid contains at the most 3/3 cells per cmm. (6,000 cases), Eskuchen (1930) regards as the maximum count of the normal fluid 9/3 per cmm., and Kafka and Samson, according to Samson (1931), obtained from a large material cell counts that were at the most 5/3 per cmm. in 89 per cent and 8/3 in 11 per cent of all the normal fluids examined. In all fluids with a cell count higher than 8/3 per cmm. they established other minor deviations which precluded the inclusion of the fluid among the normal, and they speak of an abnormal cell count when it ranges from 9/3 to 15/3 per cmm. Any value above the latter is regarded by them as pathological in every case. Demme (1935) reports 8/3 per cmm. as the maximum for normal, stating however that in one-half of the normal cases not a single cell was visible in the counting-cell and that in 86 per cent of the cases he found at the most 4/3 cells per cmm. It nevertheless is the opinion of this worker that cell counts of from 8/3 to 12/3 per cmm, need not necessarily be regarded as pathological provided that the fluid does not manifest alterations in other respects.

Apart from the cell count the nature of the cells is of significance in the evaluation of the character of the cerebrospinal fluid. The normal form of the fluid cell is a small lymphocyte, which therefore is

briefly designated herein as the fluid cell. Knick (1925) and Demme (1935) are of the opinion that the presence of some solitary neutrophil leukocytes in the fluid need not in itself be considered a pathological manifestation.

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After the first six months of a child's life have passed, its cerebrospinal fluid does not greatly differ from that of the adult. Samson (1931) made punctures on over 200 healthy children varying in age from six months to twelve years, with the following results:

Concerning the results of punctures on full weight infants during the first trimester of life excluding the first two weeks, Samson (1930) states that the normal fluid at this age does not differ in appearance from that obtained in later life. The cell count ranges from 3/3 to 15/3 per cmm. and accordingly is intermediate between the values for the newborn period and for later life.

In my own small material of full weight infants in the same age group (20 cases) I found cell counts of from 1 to 4 per cmm. (3/3—12/3). No yellow stain was observable in these fluids.

Waitz (1928) counted from 5 to 20 cells per cmm. in the cerebrospinal fluid of the full weight newborn infant when the fluid was clear. The count varied greatly in the case of blood-tinged fluids, and uniformity was not always found in its relation to the number of red blood cells. On the following days there was a marked increase in the number of cells in some cases and a sharp decline in others.

LEVINSON, GREENGARD and LIFVENDAHL (1926) frequently encountered in the fluid of full weight infants a very high cell count (from six cells to several hundred) without being able to indicate any consistency between the number of cells and the protein content. Three of the infants gave a strongly positive Wassermann reaction.

Samson (1930) found that the cell count in full weight newborn infants ranges from 3/3 to 20/3 per cmm., with an average of 10/3. It was less than 10/3 in most of the fluid specimens and high values were an exception. The cells consisted chiefly of small lymphocytes, but also a few large mononuclear cells were encountered.

In so far as premature infants are concerned I have been able to find in the literature only one investigation — that by Samson (1931) — on the cell count of the cerebrospinal fluid. He observed the fluctuations in the number of cells both during the first six months and later, but unfortunately he does not state the size of his material. He reports that the cell content of the cerebrospinal fluid of the premature infant generally exceeds somewhat that of the full weight infant. At the same time he stresses that a longer period of time is required with the premature infant than with the full weight child for the cell count to decline to normal, and that in the premature infants this process is more rapid with those of a high birth weight.

The results obtained by Samson will be best seen from Table 4.

TABLE 4

Cell Count in the Cerebrospinal Fluid of Premature Infants

According to Samson

Are in Months	Cell Count per cmm		
Age in Months	Maximum	Mean	
0-12	30/3	12 3	
12-1	15/3	10/3	
1-2	15/3	10/3	
2-3	10/3	8/3	
3-4	8/3	6/3	
46	8/3	4/3	
over 6	8/3	3 3	

Personal Investigations

In my own material I have obtained cell counts considerably higher than those of Samson. The mean cell count in the cerebrospinal fluids withdrawn in punctures made within the first 24 hours

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post partum is 7 per cmm. (5 cases). The highest number of cells counted in these fluids is 15 per cmm. and the other counts vary between 4 and 6 cells per cmm. The one extreme value thus greatly raises the average. On the second day of life the mean value remains unchanged, but a rather sharp rise occurs on the following days, and the mean cell count in the fluid of the premature infants from the second to the seventh day of life is 11. The rise continues during the second week, when my highest weekly average of 13 is attained. A rather sharp fall is noted in the following two weeks (mean value 9), and there is an even decline also thereafter, but its rafe is much less rapid than earlier.

The fluctuations in the cell count in premature infants of different ages is indicated by Table 5 and a diagrammatic presentation is given in Fig. 1.

TABLE 5

Cell Count in the Cerebrospinal Fluid of Premature Infants
Author's Investigations

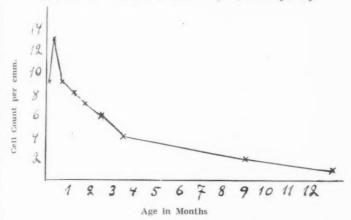
Age in Months	No. of Cases	Mean Celi Count per cmm	
01/4	21	9	
1/4	15	13	
121	30	9	
1-112	31	8	
1 1/2-2	25	7	
23	39	6	
31	10	4	
46	13	4	
612	11	2	
over 12	5	1	
Total	200		

I thus found in my material as late as in the fourth month a mean cell count of 4 per cmm. This high value was established by Samson in newborn premature infants only.

In so far as the types of cells found in my series are concerned, no neutrophil leukocytes were generally encountered.

FIG. 1

Mean Fluid Cell Count in Premature Infants, according to Age



In one case the count was 2 neutrophil leukocytes per cmm. in a total cell count of 11 per cmm. (case No. 27), and in three cases there was 1 per cmm. (cases No. 21, 69 and 86).

It is also interesting to note that in my material the high cell count persists for the longest period of time with the premature infants having the lowest weight at birth. This is seen from the table given below on the mean values in the different groups of premature infants in their second trimester of life.

TABLE 6

Mean Cell Count in Groups I—111 during the Second Trimester
Author's Investigations

Group	Weight at Birth, grams	No. of Cases	Mean Cell Count per cmm.
I	≤1,500	12	5
11	1,5012,000	6	3
III	2,001-2,500	5	2

The number of cases in each group of this comparative table is small but it nevertheless serves to clearly indicate the decline

that evenly and consistently occurs in the cell count as the birth weight of the infants increases. In group III, which comprises only five cases, the cell counts in the individual cases are already very uniform at this age, for the highest cell content in this group is 2 per cmm. The evidence supplied by this relatively small material, becomes all the more reliable because of the fact that in these cases the protein content is always consistent with the cell count, as will be described in greater detail later in this work.

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The highest cell count entered in my entire material is 44 per cmm. (case No. 24). The weight of this premature infant was 1,775 g. at birth and the child was punctured at the age of nine days, when the weight had declined to 1,370 g.

Samson (1931) regards increased meningeal permeability as the sole cause of the increase in the cell count to the levels above normal which were obtained by him in premature infants. He bases his opinion among other findings upon the regularity of the increase. He states: »Die Geburtsschädigung mag häufig sein (Ylppö, Schwart, Dollinger, Neurath), aber sie ist keineswegs die Regel. Auch weisen alle diese Kinder, deren Liquor wir soehen beschrieben haben, keines von den klinischen Zeichen auf, die wir gewohnt sind, als Ausdruck einer Hirnaffektion beim Säugling anzusehen: Asphyxie, Anfälle von Cyanose, Zuckungen, Krämpfe, Trinkunlust, Schläfrigkeit, Brechen, Fontanellenspannung.» Samson states that he regards these increased cell values as physiological and thus as fully pertinent phenomena.

A reverse point of view is entertained by Waitz, even if he regards, on the basis of results obtained by him with full weight infants, the changes in the cerebrospinal fluid as originating in aseptic meningitis. This in his opinion is due in the majority of cases to hemorrhages occurring at birth.

On the basis of my own studies and with due consideration to the findings of the above mentioned investigators that the meningeal permeability is frequently above normal in infants up to the end of the first year (Feigel, Leonow, Schippers and Peters, Schaperstein), I have reached the conclusion that unquestionably the most important factor in the causation of the high cell counts found by me in premature infants is an increase in the meningeal

nermeability. However, certain facts have evolved in my studies which speak for the probability that hemorrhages at delivery may also have a part in the causation of the higher cell count. I have found a greater number of cells during the second than during the first week of life and the same I also found to be true in regard to the protein content, as will be explained in greater detail in the following chapter (Tests for Proteins). It is in my opinion difficult to account for this finding merely on the basis of the theory of permeability, for it seems inexplicable why meningeal permeability should be higher during the second than during the first week of life. True, we might think that the altered conditions of existence in extrauterine life may produce some kind of a physiologic state of excitation in the organism, for instance due to more active metabolism and circulation of fluids, and this in turn would lead to increased permeability. However, I should expect this to take place already immediately post partum and not in the second week of life. A more natural and perhaps a better founded reason for an increase of the permeability as late as in the second week of life (assuming that we wish to adhere to the theory of permeability) probably would be the presence of neonatal icterus. The investigations of Ylppo (1913) on the one part indicate that there usually is a rise in the bilirubin content of the blood of the premature infant during the first six to ten days after birth, and on the other part the studies of Anselmino and Hoffmann to some extent speak for the possibility that icterus may increase meningeal permeability.

My finding, particularly in the case of premature infants with a low birth weight on whom a number of punctures were made at intervals of two or three weeks, that the cell count and concurrently also the protein concentration sometimes increases in comparison to the preceding puncture, when there was a decline, is in my opinion a problem which is still more difficult to solve by the theory of permeability. In my opinion, a better explanation for both the neonatal increase and this increase in the cell and protein contents is the following. In the organization of possible cerebral hemographeses a condition of local irritation is created in the cerebral membranes at the sites of the hemorrhages, in other words a mild,

slow, local meningitis sets in, causing a diffusion of cells and proteins into the cerebrospinal fluid. Such increases in these diffusions as are later encountered would thus originate in a process which has become organized later, is localized deeper, and, so to say, comes to the surface later. This concept is supported by the findings of certain investigators (Samson 1931, Demme 1935) that, following punctures which cause hemorrhage, an aseptic condition of meningeal excitation frequently arises, leading to a slight rise in the cell count and the protein content. So Herrmann (1922) found higher cell and protein contents after injection of air into the spinal canal, and Mader and Saenger (1925) an increase in the number of cells after injection of Ringer's solution into the spinal canal.

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It was because of this finding that I performed one puncture only on each premature infant in 67 per cent of the cases so that no side effects of this nature would coincide. According to the investigators last mentioned, the influence of such conditions of meningeal excitation will be present for a few days only, and therefore the high cell counts occasionally seen in my material following previous declines cannot be due to hemorrhage at the preceding puncture, for, as stated above, I held an interval between punctures of a least two weeks, the shortest interval being ten days.

It is only natural that with premature infants of a low weight at birth the meningeal permeability is greater and of longer duration than with those of a higher birth weight. From this point of view it can well be understood that the changes in the cerebrospinal fluid of the premature infants in Group I (weight at birth 1,500 g. or less) maintain the longest. This is comprehensible also on the basis of the hemorrhage theory, for hemorrhages occur more frequently in the small premature infants (Ylppö 1920, 1922, 1924, Schwartz 1924, 1927) and are more extensive than with premature infants of greater birth weight.

The correlation of the incidence of hemorrhages to the weight of the premature infant at birth is clearly shown by the following tabulation of the results of Ylppö's investigations.

TABLE 7
Incidence of Cerebral and Spinal Hemorrhages with Premature Infants
According to Ylppö

Weight at Birth	No. of Autopsies	No. of Cerebral or Spinal Hemorrhages Found		
	Autopates	No. of Cases	Percentage	
1,000 g. or less	20	18	90.0	
1,001—1,500 g	51	39	76.5	
1,501-2,000 *	17	6	35.3	
2,661—2,500 »	15	4	26.7	

It can be seen from the above table how very much more common hemorrhages are with the small premature infant.

It is a well known fact that most infectious diseases may produce a slight increase in the cell count of the cerebrospinal fluid. I am of course unable to claim that infectious diseases play no part in the cell counts in my material which were above normal, although every effort had been made by me to select the material also with due regard to this point. However, I am reluctant to believe that the increased cell count, which continued up to the second week of life, could be solely attributable to infection. The sharp decline which took place already in the third week argues against this view, for it would only be reasonable to believe that a possible increase in the cell count caused by infectious diseases would be greater in the third week than in the second, as a longer stay in the premature infant ward offers increased possibilities for infection even if every precaution is taken. Theoretically, at least, the prevention of infection is easier for two weeks than for three. The regularly declining trend which I noted in the cell count in the following weeks also gives reason to assume that infection is not a significant contributory factor, for, as my material is not very large in any of the groups, the presence of an external factor would readily manifest in irregular declines and unexpected increases of the cell count in the different groups.

I have very little to say in so far as the number of red blood cells is concerned. In two cases only the erythrocyte count was sufficiently high to produce a slight turbidity in the fluid, being about 860 and 460 cells per cmm. respectively (cases No. 5 and 25). According to Samson (1931) one to two leukocytes correspond to 1,000 erythrocytes in blood-tinged cerebrospinal fluids. Accordingly, in the case of the two fluid specimens mentioned, one cell only should be deducted from the white blood cell count in order to obtain the true leukocyte count. In addition to these two cases there were five cases with an erythrocyte count over 50 but not over 170, whereas in 134 cases not a single erythrocyte or only one was found.

From the number of erythrocytes present in the specimens of cerebrospinal fluid collected by me the conclusion can be drawn that the performance of punctures even on subjects as small as premature infants is, given a good technique, definitely possible in the majority of cases without hemorrhage being produced.

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Although not specifically in reference to premature infants, a minor point may here be mentioned. In the literature one frequently encounters the term scell count normals but it may later appear from the text or the case reports that the number of cells per cubic millimeter is as high as 10 or even 15 (or 30/3 and 45/3 respectively), which definitely must be regarded as exceptions to the normal. To avoid such conflicting statements it would be advisable to state in these cases the actual cell count, which is just as brief to express yet more explicit.

In my investigations I find that the cell count in the cerebrospinal fluid of the premature infant is considerably higher than the normal count and moderately higher than even that of the full weight newborn infant. With the premature infants of a low birth weight the cell count remains elevated for a longer period of time than with those of a higher weight at birth.

I therefore draw the conclusion that this elevated cell count is produced by an increased meningeal permeability in the premature infant. However, I regard it as highly probable that in certain cases a condition caused by cerebral hemorrhage occurring at delivery may be a contributory factor. The cell count of the cerebrospinal fluid, however, cannot in my opinion be employed as an indication of the presence or absence of cerebral hemorrhage which may have occurred sub partu.

VIII. Tests for Proteins in the Cerebrospinal Fluid of the Premature Infant

1. Pandy's Reaction

For determination of the increase in the protein content of the cerebrospinal fluid the carbolic acid and ammonium sulfate reactions developed by Pandy and Nonne have been continually employed. These were originally devised to give a negative reaction on normal fluid. It has been found, however, that Pandy's reaction may sometimes show a barely visible opalescence under fully physiological conditions (Samson 1931, Demme 1935).

Levinson (1928) reports 57 positive and 43 negative reactions from specimens of the cerebrospinal fluid of 100 full weight newborn infants. Samson (1931) states that the reactions on full weight newborn infants are always positive, frequently strongly positive. In fluids withdrawn from full weight infants during the first trimester of life with the exception of the newborn period, Samson found \pm or + reactions, and during the second trimester negative reactions only or at the most a faint opalescence. After the first six months Pandy's reaction is always negative according to Samson.

In a small material comprising 20 full weight infants I found a few weakly positive Pandy's reactions during the first trimester excluding the first two postnatal weeks. In the majority of cases, however, the reaction was negative.

In comparing the protein in the fluid of full weight infants with that of premature infants Samson states in reference to the latter: »Auch die einfachen Eiweissreaktionen haben einen etwas stärkeren Befund.»

Personal Investigations

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In my own premature infant cases I saw a number of very strongly positive Pandy's reactions; this was in particular the case with the newborn. The reaction, furthermore, continued to be positive for an unexpected length of time. The degree of intensity of the reaction in the different age groups in my material is shown in the following table.

TABLE 8

Pandy's Reaction from the Cerebrospinal Fluid of Premature Infants

Author's Investigations

Age in Months	No. of Cases					
	Total	+++	++	+	±	-
0-1/2	36	21	14	1	0	- 11
0—½ ½—1	30	3	22	5	0	()
1-2	56	2	24	29	1	()
2-3	39	0	14	22	3	(1
3-4	10	0	3	6	1	()
46	13	0	0	10	0	3
6-12	11	0	0	2	2	7
over 12	5	0	0	1	0	4
Total	200	26	77	76	7	11

With the newly born, Pandy's reaction was in the majority of cases strongly or very strongly positive. With one newborn only I found a simples positive reaction. As is seen from the table, the first fully negative responses were not found until after the fourth month of life, even if the age group of four to six months reveals ten positive reactions out of thirteen specimens. After the first six months have passed, the greater part of the fluids are Pandy negative; however, one premature infant over one year of age still gave a positive reaction (case No. 96). The birth weight of this infant was 1,750 g. and it was punctured at the age of 1 year 5 days, when the weight was 9,560 g.

It is to be regretted that in order to save specimens of fluid for other tests I was unable to carry out Nonne's reaction on more

than about 10 per cent of my material, and no definite statement can therefore be made on the results of this test. On the whole, they were most frequently positive in the first trimester but later mostly negative.

2. Quantitative Protein Determinations

Quantitative determination of the protein content of the cerebrospinal fluid has lately gained increased approval. Most investigators report from 15 to 30 mg. per cent as the protein content of the normal cerebrospinal fluid of the adult, the amount of albumin being higher than the amount of globulin. The ratio of globulin to albumin is normally 0.20: 0.45 (DEMME 1930, 1935).

According to Samson (1931) the amount of protein in the fluid in childhood after the first six months does not differ in any way from that in the adult. He gives the following values for children:

PFAUNDLER found in children values which varied from 20 to 40 mg. per cent and usually were 30 mg. per cent. Waitz (1928) states that the amount of total protein in full weight newborn infants fluctuates between 30 and 100 mg. per cent when the fluid

TABLE 9

Protein Content in the Cerebrospinal Fluid of Full Weight Infants in the First
Six Months
According to Samson

Age in Months	Minimum and Maximum Values in mg. per cent	Mean Value in mg. per cent
0-1/2	4080	60
1/2-1	30-50	40
1-2	24-46	32
2-3	20-40	26
3-6	16-36	24

is clear. During the first six months Samson (1930) encountered in full weight infants the values listed in Table 9, calculated from 15 to 30 cases in each age group.

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In my studies on full weight infants I found that the protein content of the cerebrospinal fluid in the first trimester of life excluding the first two weeks ranges from 19 to 38 mg. per cent, with an average of 30 mg. per cent (20 cases mentioned above). These results fairly closely approximate those of Samson, even if the values are slightly lower.

In so far as the protein content of the premature infant's cerel-rospinal fluid is concerned I have found in the literature no studies other than those of Samson (1931). It is to be regretted that also in this case he omits to state the size and composition of his material.

Samson obtained the results shown in Table 10.

TABLE 10

Protein Content in the Cerebrospinal Fluid of Premature Infants
According to Samson

Age in Months	Mean Value of Total Protein in mg. per cent
01/2	60
121	50
1-2	46
2-3	35
3-4	30
46	24
over 6	20

Personal Investigations

Consistently with my findings of a cell count which is higher than that ascertained by Samson, I also obtained considerably higher values for the protein content of the cerebrospinal fluid. In one of the cases I found as high an amount as 269 mg. per cent

of protein. The weight of this infant (case No. 32) was 1,700 g, at hirth and 1,760 g, at the time of punteure at 14 days. In another case (No. 34) the amount of protein was 212 mg, per cent, the puncture being also performed at the age of 14 days. In a third case the value of 187 mg, per cent was obtained. This infant (case No. 30) had a birth weight of 1,300 g, and was punctured at 11 days; its weight was then 1,130 g. All of these high values, however, were exceptional, for in all the other cases a very much lower level prevailed, the following high value being 137 mg, per cent.

In respect to the protein content a similar development was observable as in the cell count, i.e. an increase occurred in the first and second weeks of life, the maximum values being then reached, followed by a rather sharp decline which later continued at a much slower rate. It is seen that the increases and decreases in the cell count and the protein content always take a closely concurrent course.

The variations in the amount of protein found by me in the different age groups are best illustrated by Table 11 and Figure 2.

TABLE 11

Protein Content in the Cerebrospinal Fluid of Premature Infants
Author's Investigations

Age in Months	No. of Cases	Mean Value of Total Protein in mg. per cent	
0	19	100	
1/41/2	13	128	
1/21	30	75	
1-112	31	66	
112-2	24	62	
2-3	36	54	
3-4	10	50	
46	13	42	
612	10	30	
over 12	5	28	
Total	191		

FIG. 2 Mean Fluid Protein Content in Premature Infants, according to Age

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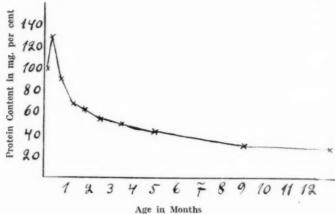
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A comparison of this graph with that on the cell count immediately reveals a marked similarity in the two curves (page 43).

On the other hand a comparison of the results of Samson's investigations with the values obtained in my material indicates that the highest mean values in Samson's material (newborn infants) correspond with the mean values found in my material at the turn of the second and third months.

The correlation between the weight at birth and the protein

TABLE 12

Protein Content in the Cerebrospinal Fluid of Premature Infants during the Second Trimester

Author's Investigations

Group	Weight at Birth, grams	No. of Cases	Mean Protein Content in mg. per cent
1	≤1,500 g.	12	50
II	1,501-2,000 »	6	45
III	2,001-2,500 »	5	34

content of the cerebrospinal fluid is clearly indicated by Table 12 which gives the mean values in the different weight groups for the second trimester of the infants' life.

The number of cases analyzed is small, but on the other hand the individual values established in each group are rather uniform already at this age and thus impart even to this small material a fairly great degree of evidence. This is further enhanced by the regularity of the decrease in the cell count in the same material, as discussed in the preceding chapter (Cell Count).

My material thus indicates that protein values above the normal are still found in the second trimester even in the largest premature infants (group III). In the latter half of the first year, elevated protein values generally are no longer encountered in group III, although this is the case with the premature infants of a low birth weight (groups I and II). Values somewhat above the normal may be seen in children in the latter two groups even as late as at the beginning of the second year, as for instance in case No. 96 cited above (Pandy's Reaction). This child (weight at birth 1,750 g.) still had 44 mg. per cent of protein in the cerebrospinal fluid at the beginning of the second year.

Comparing the results of Pandy's reaction and of the quantitative protein determinations in my material we find that an amount of 25 mg. per cent of protein results in a negative reaction, even if it sometimes may give a positive response. When the level of 70 mg. per cent is approached, + + Pandy's reactions begin to be registered. Just before 100 mg. per cent + + reactions are mostly obtained.

It has been revealed in my investigations that the protein concentration of the cerebrospinal fluid of premature infants is very much higher than that of full weight infants. My values, furthermore, greatly exceed those established by Samson.

It seems natural and readily explicable that the elevated protein levels are produced by the same factor as the elevated cell count. Samson is of the opinion that the increased protein content ascertained by him is due solely to a meningeal permeability which

is above the normal limits. For my part I regard the increased permeability as the most important factor in the high protein values obtained in my investigations, but I also deem it probable that cerebral hemorrhage may have been a contributory cause in certain cases. This opinion is supported by the investigations referred to in the preceding chapter (MADER and SAENGER, SAMSON, DEMME) on the creation of a state of meningeal excitation by a hemorrhagic puncture or by a foreign substance (Ringer's solution) injected into the spinal canal. It is also supported by HERRMANN's finding of an increased protein concentration following injection of air into the spinal canal. Samson, again, encountered high albumin values in the cerebrospinal fluid a few times as late as eight and eleven days after encephalography (30 and 40 mg, per cent respectively) whereas prior to the taking of the encephalogram a normal protein content was established. Similarly, after injections of serum Samson found an increase first in the cell count and then in the protein content of the cerebrospinal fluid. The high protein level maintained for a greater length of time than the elevated cell count.

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There may be reason to point out in this connection that the results obtained by Waitz probably cannot be regarded as fully reliable in respect to the cell and protein contents in view of the fact that his punctures were made at very brief intervals and that hemorrhages were reported by him in over one-half of the cases.

I must leave open the question why I have obtained higher values than Samson for both the cell count and the protein content of the cerebrospinal fluid of premature infants. This cannot be attributable to the methods employed by me, as my results for the full weight infants in the first trimester conform well with those obtained in Samson's corresponding investigations. In fact, the values for the cell count and for the quantitative protein content are in my latter study slightly below those of Samson.

In the present studies I have found that the protein content of the cerebrospinal fluid of the premature infant is higher to a marked degree than that of the normal cerebrospinal fluid and to a fairly great degree than that of full weight infants. These high values maintain for a longer period of time with the premature infants of a low birth weight than with those of a higher birth weight. I regard

the increased meningeal permeability of the premature infant to be the chief cause of this excessively high protein content, but at the same time I consider it highly probable that in certain cases cerebral hemorrhage occurring sub partu may be a contributory factor.

3. Tryptophan Reaction

The normal cerebrospinal fluid gives a negative tryptophan reaction.

Investigators who have studied the presence of tryptophan in the cerebrospinal fluid under various pathological conditions have obtained results which are unusually consistent. All these workers have found the tryptophan reaction to be very often positive in tuberculous meningitis (in from 90 to 100 per cent of the cases). Most investigators report occasional findings of a positive reaction also in some cases of purulent meningitis, such as meningopneumo-, staphylo- and streptococcal meningitis. Some of the workers did not find in these cases a pure violet ring but one of a grayish shade of violet, and they call this a pseudopositive reaction.

Lichtenberg (1932) obtained a positive response in two newborn infants. In both cases severe cerebral hemorrhages were later encountered at autopsy.

A tryptophan reaction was carried out in all cases of diagnosed or suspected tuberculous meningitis entered at the Helsinki Municipal Epidemic Hospital in the years 1937—1940. It was also made in most cases of purulent meningitis, in numerous cases of poliomyelitis, and frequently in conditions of aseptic meningitis associated with various infectious diseases (morbilli, parotitis epidemica, scarlatina, etc.). The number of cases in which the reaction was performed totaled over 200, and about 10 per cent comprised tuberculous meningitis. All of the latter cases gave a positive reaction, even if not always at the onset of the disease. A positive reaction was also obtained in one case each of streptococcic, influenzal and pyocyanic meningitis. The last mentioned case gave a remarkably high protein content (625 mg. per cent) and the tryptophan reaction was very strong. Negative reactions were obtained in all cases of poliomyelitis as well as of aseptic meningitic

conditions associated with infectious diseases. I have thus obtained results which conform with those of other investigators, as they demonstrate that a positive tryptophan reaction obtained from clear cerebrospinal fluid is a strong diagnostic indication of tuberculous meningitis.

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Personal Investigations

I performed a tryptophan reaction from 57 specimens of cerebrospinal fluid taken from 37 premature infants. A single reaction was made in the case of 23 infants, and several reactions in 14 infants who were punctured more than once, as follows: Four reactions in two cases, three in two cases, and two in ten cases. If a positive reaction was obtained from the first puncture I endeavored to make the test also from subsequent punctures until it became negative.

A general survey of the results of the tryptophan reaction carried out in my present work is given in Table 13.

TABLE 13

Tryptophan Reaction from the Cerebrospinal Fluid of Premature Infants
Author's Investigations

Age in Months	No. of	1	Reactions	
Age in months	Specimens	+	±	
01/2	18	12 (67%)	1	5
(01/4)	(12)	[11 (91%)]	(0)	(1)
1/2-1	12	3 (25%)	3	6
1-2	21	0	7	14
over 2	6	0	0	6.
Total	57	15	11	31

I have indicated as \pm a reaction in which a violet ring is produced but is very narrow.

A finding of interest in my opinion is the large number of positive reactions obtained in premature infants under one month of age, for of the twelve infants punctured in their first week as

many as eleven responded positively (figures given in parentheses in the table). The relatively early change to the negative I find to be another remarkable phenomenon. Thus I did not find a single distinctly positive reaction in children from one to two months of age, but one-third of the cases still gave a \pm reaction. The latter reaction already disappeared completely after the age of two months.

I have been unable to find in the literature any record of tryptophan reactions carried out with the cerebrospinal fluid of premature infants. Samson (1931) states as his opinion, based on other studies on proteins, that qualitatively the protein in the cerebrospinal fluid of the newborn infant — including the premature — does not differ from that present in later life. However, the numerous positive tryptophan reactions which I obtained in newborn premature infants constitutes evidence against this inference. The relatively early change to negative described above supports for its part the concept that the proteins in the cerebrospinal fluid of the newborn premature infant qualitatively differ at least to some extent from those encountered in later life. It probably is difficult to render any other interpretation to the positive tryptophan reactions which I obtained.

I frequently observed in my tests fairly high protein values, particularly in the first month of life of the premature infant. It is a known fact that the protein concentration generally is fairly high also in tuberculous meningitic conditions. It could therefore be assumed that the positive tryptophan reaction would result merely from the high protein content because of a sufficient amount of tryptophan being included in these total protein amounts to produce a positive reaction. However, this probably is not the case. The protein content is frequently very high also in conditions of purulent meningitis, yet the reactions often are negative. I also found in the cerebrospinal fluid of poliomyelitis patients moderately high amounts of proteins, whereas the tryptophan reaction gave a negative reading. In five cases of my material of premature infants I also obtained a negative response in a specimen taken at a later puncture although the protein content in two cases was equally high as and in three cases even higher than in the preceding

puncture, which had given a positive reaction (cases No. 1, 11, 13, 19 and 50). In the quantitative studies I did not find the highest mean protein values for the entire material until in the second week, when positive tryptophan reactions already were considerably more infrequent than in the first week.

Especially in cases where premature infants are the subject of study due consideration should be given to the possibility that a positive tryptophan reaction may be the result of cerebral hemorrhage occurring at delivery. Of interest in this connection is the above mentioned report by Lichtenberg on the positive tryptophan reactions obtained in two full weight newborn infants in whom severe cerebral hemorrhages were encountered at subsequent autopsy. In my own material of premature newborn children I encountered fairly large cerebral hemorrhages in three cases that had given a positive tryptophan reaction (No. 3, 5 and 6). The individual evidence of these cases is diminished by the fact that cerebral hemorrhages are very common with premature infants. On the other hand it may be possible that the proteins in the cerebrospinal fluid of also the full weight newborn differ somewhat in a qualitative respect from those of later life. Lichtenberg's two positive reactions probably can also be explained against this background.

Taking into consideration that out of twelve premature infants in my series punctured during their first week of life eleven gave a positive tryptophan reaction, the incidence of cerebral hemorrhages would be extremely high were the postive tryptophan reaction produced by cerebral hemorrhage. According to the autopsy material of Ylppö, cerebral hemorrhages — even in premature infants of a low birth weight — are not as frequent as this would indicate.

The youngest premature infant who was punctured in my series and from whose cerebrospinal fluid the tryptophan reaction was made was three hours old (case No. 1). There were two other cases punctured within the first 24 hours (cases No. 3 and 5) and two punctured within the first 48 hours (cases No. 6 and 8). All five reactions were positive. A change to the negative had already taken place when a second specimen was drawn at the age of 14 days

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from the infant first punctured at three hours. Similarly, the positive reaction of one of the two infants punctured at the age of one day had become negative when a second puncture was made at 17 days (case No. 8).

On the basis of positive tryptophan reactions obtained by me immediately post partum I regard it as probable that the causative factor of such reactions exists already in intrauterine life.

To resume, I very frequently obtained a positive tryptophan reaction from the cerebrospinal fluid of the newborn premature infant; this was particularly the case in the first week of the infant's life.

The results of my studies on the tryptophan reaction are in my opinion evidence indicating that the proteins in the cerebrospinal fluid of the newborn premature infant at least to some extent differ qualitatively from those present in later life.

4. Mastic Reaction

Opinions diverge on the theoretic aspect of the mastic reaction. However, a discussion of the theory is not called for here, and I confine myself to the statement that recent research has proved the correctness of the earlier findings by Emanuel (1915), Goebel (1921, 1924), Kafka (1921) and Sahlgren (1922) to the effect that the nature of the proteins present in the substance under test is of decisive significance in the production of the mastic reaction. However, also the saline and hydrogen ion concentrations are of contributory importance in the processes of turbidity and precipitation.

Skliar (1928) has sought to determine possible differences in the mastic reactions made from adult and infant cerebrospinal fluids. His investigations reveal no differences in this respect.

Samson (1931), who in his investigations employed Kafka's normomastic reaction exclusively, has studied the reaction in the cerebrospinal fluid of the child and reports negative reactions throughout childhood, including also the newborn period with its elevated protein content. In the majority of cases Samson found a slight turbidity in the third or the fourth tube. With the newborn this occasionally was not recognizable until in the fifth tube.

This, according to Samson, is also the response in the premature and full weight infants in whom no cerebral hemorrhage has occurred at birth, whereas infants — both premature and full weight — with cerebral hemorrhage give a positive normomastic reaction. Samson states: »Der Ausfall kann sehr ausgeprägt sein, meist ist er jedoch schwach aber deutlich. Wir schliessen aus ihm auf eine Geburtsschädigung auf Grund der zahlreichen völlig negativen Befunde und der Tatsachen, dass solche Kinder eine Reihe klinischer Zeichen aufgewiesen haben. Die Eiweisswerte sind dabei verschieden gross. Sind sie höher als die von uns angegebenen Normalzahlen für dieses Lebensalter — das kann in beträchtlichem Masse der Fall sein — so finden wir auch ganz erhebliche Abweichungen des Maximums der Normomastixkurve nach rechts.»

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Personal Investigations

The material on which I performed the mastic reaction is unfortunately a small one, consisting of 22 reactions only. Furthermore only one of the reactions was made from the fluid of a newly born child. The principal reason for the smallness of this material is the greater importance which I placed upon certain other aspects of the investigation, and therefore in many cases a sufficient amount of cerebrospinal fluid was not available for the mastic reaction.

A classification of this material according to age is given below. I have regarded as positive a reaction in which any tube shows pronounced turbidity or slight precipitation (2), or pronounced or

TABLE 14

Malerial Used in the Mastic Reaction
Author's Investigation

Age in Months	No. of Cases
0—1	10
1-2	6
2-3	4
over 3	2
Total	22

complete precipitation (3 and 4) (cf. page 20). Classified according to this criterion there were ten positive and twelve negative responses in my material.

Of the ten positive reactions obtained, eight were in premature infants punctured before the age of one month and two in infants punctured at one to two months of age. All punctures on premature infants over two months old produced a negative response. I found very pronounced precipitation (444422) in a specimen drawn from the only newborn infant in this material. At subsequent autopsy this infant, whose cerebrospinal fluid was entirely clear, was found to have fairly extensive hemorrhages in the leptomeninges. The child's weight at birth was 1,300 g. and it was punctured at the age of one day, the weight then being 1,260 g. (case No. 6, cited above in connection with the tryptophan reaction). In all the other cases of positive reaction I found turbidity or precipitation in the third or the fourth tube, or in both, with the exception of one case in which the second and third tubes already were cloudy. In two cases only, apart from case No. 6 described above, the reaction was rather strong, i.e. case No. 1 (002310) and case No. 53 (113210). No oclinical symptoms of cerebral hemorrhage were present in these cases. Two weeks later the mastic reaction was negative in the latter case, although in the meantime the quantitative protein content had increased from 62 to 75 mg. per cent.

Among the negative reactions I particularly wish to point out case No. 11. This infant, whose weight at birth was 1,570 g., was punctured at the age of 34 days. Pandy's reaction from the fluid specimen was very strongly positive, the protein content was 137 mg. per cent, and the cell count 39 per cmm. Regardless of these high cell and protein values the mastic reaction was negative. At the same time the tryptophan reaction was negative despite its having been positive a month earlier, when the protein content was smaller (112 mg. per cent). It is my opinion that the high protein content and cell count in this case apparently are in part due also to cerebral hemorrhage.

My own investigations on the mastic reaction prevent me from concurring in Samson's opinion, based on the normomastic reaction, that the mastic test can serve as an indication of the presence or absence of cerebral hemorrhage at delivery. Samson infers, furthermore, from the negative normomastic reactions obtained by him in the newborn, including the premature, that the proteins in the cerebrospinal fluid of the newborn infant are qualitatively exactly similar to those of the older child and that their composition thus is identical. I must take a divergent point of view also in this regard, for on the basis of my own investigations I regard it as probable that the proteins in the premature infant's cerebrospinal fluid in the first month of life and particularly in the newborn period frequently differ qualitatively, at least to some degree, from the proteins present in the fluid in later life. I hold that my opinion is also supported by the marked concurrence of the mastic and tryptophan reactions observed in my investigations.

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I thus frequently obtained in my studies a positive mastic reaction from the cerebrospinal fluid of the premature infant during the first month of life. This in my opinion corroborates the opinion formed upon the results of my tryptophan reaction that the proteins in the cerebrospinal fluid of the premature infant in the first month of life and particularly in the newborn period frequently differ qualitatively to some extent from the proteins present in the cerebrospinal fluid in later life.

IX. Sugar Content in the Cerebrospinal Fluid of the Premature Infant

The sugar content of the adult cerebrospinal fluid has been the subject of numerous studies. According to most investigators the average amount of the sugar is approximately 60 mg. per cent (from 55 to 70 mg. per cent). In meningitic conditions these values are greatly below normal, but in encephalitic conditions mostly above normal. Comparative studies show that even in normal cases the ventricular fluid has a definitely greater sugar content than the lumbar fluid (Weigelt 1921, Cestan, Riser and Laborde 1923, Kafka 1930, Samson 1931). A certain relation has been found to exist in general between the sugar content of the cerebrospinal fluid and that of the blood, and for this reason most investigators recommend simultaneous determination of the two sugar concentrations, preferably after the subject has fasted for several hours.

Graysel and Orent (1927) found that following a parenteral dose of sugar the sugar concentration of the blood reaches its maximum 27 minutes later and reverts to normal in three and one-half hours, whereas that of the cerebrospinal fluid does not attain maximum until two and one-half hours after the administration of sugar and reverts to normal six to seven hours after the administration. The subject would thus be required to abstain from nourishment for at least six to seven hours prior to puncture in order that the sugar in the fluid would be free from possible influence of the nourishment. Samson (1931) points out, however, the difficulty of observing this interval in acute conditions and particularly in the case of children, and he states that he has observed no very

marked effects exerted by nourishment upon the sugar content of the fluid. He writes: »Tatsächlich ergibt sich trotz aller Bedenken eine hohe Brauchbarkeit auch der Ergebnisse die am nicht nüchternen Kinde gewonnen worden sind.»

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The results obtained by a number of investigators indicate that in childhood, after the first six months, the cerebrospinal fluid sugar values do not generally vary appreciably from those obtained in the adult.

According to Samson the amount of sugar in the cerebros sinal fluid of children after the first six months of life varies between 55 and 70 mg. per cent. In only a part of the cases in this material the puncture was preceded by fasting. The values obtained were distributed as follows among the cases in his material:

Sugar content 60 to 65 mg. per cent in 70 per cent of the cases

Samson states that the highest values for sugar were found in cases of Little's disease and following convulsions, without any other exceptional features being noted in the fluid.

Study of the cerebrospinal fluid sugar in infants under the age of six months has been relatively meager. Levinson (1928) reports great variations (from 45 to 95 mg. per cent) in the sugar concentration in full weight infants during the first six months of life, and Samson (1931) also found great fluctuations in that of full weight newborn infants. In the second and third months of life, according to Samson, the values already are limited to from 55 to 70 mg. per cent; in 60 per cent of these cases they are between 60 and 65 mg. per cent. After the third month they are from 60 to 65 mg. per cent in 70 per cent of the cases.

I have been able to find but few records of such investigations focused on the premature infant. Samson (1931) merely mentions that fluctuations are greater with them than with full weight infants but he reports no figures. He also omits to state the size of his material.

Liebe (1940) carried out comparative determinations on the sugar content of the blood and the cerebrospinal fluid in the mate-

rial comprising both premature and full weight infants on which he conducted also the comparative bilirubin tests referred to above. He classified the material into two groups as follows:

- A) 111 cases which he regards as free from cerebral hemorrhage,
- B) 33 cases with cerebral hemorrhage(1).

In the first group the tests for blood sugar gave a mean value of 79 mg. per cent and those for fluid sugar a mean value of 56 mg. per cent. In the latter group the figures were 82 and 58 mg. per cent respectively. In the two groups the blood sugar/fluid sugar ratio was 1:0.71, which Liebe stresses as evidence of the futility of using comparative tests for the two sugar contents to indicate the presence of cerebral hemorrhage occurring sub partu. Liebe states that in eight of the cases in group A he found a higher sugar concentration in the fluid than in the blood.

Personal Investigations

One naturally is reluctant to keep a tiny premature infant without nourishment for many hours, while, on the other hand, it has been my effort in these studies to allow the sugar brought into the organism by nourishment to influence the test results as little as possible. Therefore, by combining with practical requirements the standpoints dictated by the results of the investigations of Graysel and Orent I devised the following procedure. After a fast of about five hours during the night the premature infant was given its first meal at 4 or 5 a.m. The test for sugar in the blood was taken at 8 a.m., when, according to the last mentioned investigators, the effect of the meal upon the blood sugar had passed. I then made the lumbar puncture one hour or sometimes two hours later, when the effect of the meal upon the fluid sugar could practically be regarded as past. By that time the smallest infants had already received their second meal immediately prior to the lumbar puncture, but according to these investigators it could as yet occasion no rise in the sugar content of the fluid. If no simultaneous test for blood sugar was made, I performed the lumbar puncture independently of the meals.

The values obtained in my tests for sugar in the cerebrospinal fluid are best shown by Table 15.

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TABLE 15

Sugar Content in the Cerebrospinal Fluid of Premature Infants in the First
Trimester of Life

Anthor'c	Investigations

Age in Months	No. of Cases	Mean Sugar Content in mg. per cent	Minimum and Maximum Values
0-1	21	78.6	64106
(0-1/2)	(8)	(83.0)	(66106)
1-2	16	78.0	62 96
2-3	14	74.9	60 84
Total	51	77.4	60106

Table 16 lists the results of the tests in which simultaneous determinations for sugar were made from the cerebrospinal fluid and the blood.

TABLE 16

Simultaneous Tests for Sugar in the Cerebrospinal Fluid and the Blood of Premature Infants in the First Trimester

Author's Investigations

Age in	Ago in	No. of	Mean Sugar Content		No. of Cases with Higher Fluid Sugar
Months	Cases	Cerebrospinal Fluid	Blood	than Blood Sugar Content	
01	16	81.1	77.7	9	
(0-1/2)	(6)	(87.0)	(83.0)	(3)	
1-2	5	77.6	85.8	2	
2-3	5	72.0	72.8	2	
Total	26	78.7	78.3	13	

I thus found rather high sugar values in the cerebrospinal fluid of the premature infants in the first trimester of life, whereas they were somewhat low in the blood. A fact which in my opinion is particularly worthy of note is the nearly equal level of the total

mean sugar values in the fluid and the blood, and the higher concentration of sugar in the fluid than in the blood in nearly one-half of the cases in which simultaneous determinations were made. It is to be noted, however, that the mean value for fluid sugar exceeds that for blood sugar during the first month of life only and never later within the period investigated.

The material listed in Table 15 includes cases in which the puncture was not preceded by special fasting. Regardless of this the total mean fluid sugar value in this table is slightly lower than that in Table 16. This finding corroborates Samson's statement that complete abstinence from nourishment preceding the puncture is not necessarily required in order to obtain fairly usable values in clinical work.

The somewhat low blood sugar values obtained in my study were no surprise to me, for van Creveld (1929) also found low values. i.e. between 70 and 65 mg. per cent, in the first months of life of the premature infant. In the first two months he obtained values under 70 mg. per cent in over 65 per cent of the cases and under 65 mg, per cent in over one-half of the cases. In his opinion the low sugar content of the blood is first and foremost due to the immaturity of the liver. McKittrick (1940) also obtained low blood sugar values in full weight newborn infants, these being on an average from 40 to 50 mg. per cent in the first week and from 80 to 90 mg. per cent in the second week. In this country REEN-KOLA (1941) carried out tests for blood sugar in full weight newborn infants one-half hour post partum and found that in infants with a high birth weight (minimum 4,000 g.) the blood sugar content is lower than in those weighing less than 4,000 g. at birth, the mean value for the former being 59 and for the latter 69 mg. per cent. In any case, the values are low in both groups.

My series is too small to permit our drawing any far-reaching conclusions. I further regret that the Hagedorn method was not available to me for the sugar determinations, as this probably is the best procedure now in use. In view of these facts I do not desire to claim for my figures statistically conclusive evidence even as mean values. However, my results justify the statement that the sugar content of the cerebrospinal fluid of the premature

infant during the first trimester exceeds the normal sugar content of the fluid, and when compared with the corresponding sugar content of the blood it very closely approaches the latter. The column for minimum and maximum values for the fluid sugar given in Tahle 15 above also clearly indicates how much greater those variances in value are which occur shortly after birth than those occurring in later months. So the values in the third month already maintain a level between 60 and 84 mg. per cent (14 cases). Another interesting finding is the regular decline in both the minimum and the maximum values as the children advance in age. The greatest variations in my material are found with the premature infants of the lowest birth weight. I obtained the highest sugar value of all the cerebrospinal fluids tested in my material (106 mg. per cent) from an infant who had a weight of 1,600 g. at birth and was punctured at the age of five days, when the weight was 1,560 g. The concentration of sugar in the blood was at the time 80 mg. per cent (case No. 15).

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In seeking the reason or reasons for the rather high sugar values which I obtained in the specimens of cerebrospinal fluid collected from premature infants in their first trimester, meningeal permeability could be regarded as the most probable cause. I already found it to be the principal factor in the causation of the increased protein and cell concentrations established in my tests. Indeed, it seems to me quite obvious that also my elevated sugar values are. at least to a great extent, produced by the increased permeability. In the first place these values are higher immediately post partum than at any later time, when also the permeability has decreased. and, secondly, the values are higher with premature infants of a low birth weight, who apparently also have the highest permeability. LAHDENSUU (1947) has by actual experiments demonstrated an increased permeability for sugar in infants. Following an intravenous injection of a 50 per cent solution of glucose, usually in an amount of 10 cc., he noted that the sugar content of the cerebrospinal fluid was somewhat increased, and following a similar intralumbar injection he found an unexpectedly great increase in the blood sugar values.

The elevated sugar concentration of the cerebrospinal fluid

observed by me readily raises the question of its possible significance in the development of the premature infant and particularly of its brain. The so-called megacephalic condition (YLPPÖ), common especially with premature infants of the smallest size, also comes to mind in this connection. In comparing the size of the premature infant's head with its other body measurements the disproportionately large size of the head is always noticed. When the child is approximately from six to eight months old the head, according to Ylppö, has attained its greatest size in relation to the length of the body or to the breast measurement. Earlier, therefore, hydrocephalus was believed to be present in this case, but by means of numerous autopsies Ylppö demonstrated that in the great majority of cases no particular dilatation of the lateral ventricles could be found and that the case merely was one of a relatively large brain, the consistency of which was approximately normal. Ylppö states: »Trotz der starken allgemeinen Wachstumshemmung, die ich bei den kleinen Frühgeburten festgestellt habe, hat sich das Gehirn ungestört weiter entwickelt. Das Gehirn der Frühgeburten scheint somit in seinem Wachstum eine von äusseren Umständen und extrauterinen Schädigungen vollkommen unabhängige Selbständigkeit zu wahren.» The brain of the premature infant thus follows its own laws of development.

It may be possible, in my opinion, that the high sugar concentration of the cerebrospinal fluid plays a part in this disproportionately active growth. Thus sugar would constitute the essential building and nourishing material for the brain tissue or at least function in the manner of a catalyst of some kind in the formation of brain tissue. In Kafka's opinion the sugar present in the cerebrospinal fluid should be regarded in general as nourishment for the brain tissue. This seems to be corroborated by the fact that under normal conditions the concentration of sugar is according to many investigators greater in the ventricular fluid than in the lumbar fluid, although the cell and protein contents of the ventricular fluid are lower than those of the lumbar fluid (cf. above).

On this basis it could also be regarded as possible that the high sugar values of the cerebrospinal fluid would not be a result of increased permeability alone but that the brain tissue also would

have at its disposal certain factors which make the retention of sugar possible. This would form a natural explanation for the cases in which the sugar content of the cerebrospinal fluid greatly exceeds that of the blood, as for instance case No. 15 described above, in which the former was 26 mg, per cent higher than the latter. If permeability is high in both directions and the amount of sugar in the cerebrospinal fluid is higher to a marked degree than that in the blood, the sugar, theoretically considered, should be reconveyed from the fluid into the blood. The hypothesis of a sugar-retaining capacity of the brain tissue which I presented above would then seem comparable to the phenomenon encountered in the relation of the mother and the fetus in gestation, in that the fetus takes from the mother all that it requires without regard to her condition to any great extent. This was observed particularly under recent wartime conditions when in spite of the undernourished condition of the mothers the children born were generally of a normal weight.

Apparently also for other reasons the sugar requirement of the newborn infant is relatively great. The low fluid sugar values in the newborn including the premature established by several investigators are in my opinion explicable by the fact that the organism rapidly consumes the substances that it severely needs. Even with infants of a very high birth weight the blood sugar values have been found to be low (Reenkola). Moreover, there apparently exists an exceptionally high sugar requirement in the premature infant, who during the too brief intrauterine life was not able to obtain from the mother's organism sufficient amounts of the building material which it needed.

I have accordingly found that the cerebrospinal fluid of the premature infant contains a fairly high concentration of sugar, particularly in relation to the concentration present in the blood. The cerebrospinal fluid sugar values are the highest in infants under one month of age, in whom according to my investigations the mean value may even slightly exceed the corresponding mean value of the blood sugar. As the main cause of the relatively high fluid sugar values found in my series I regard the increased permeability of the hemaloencephalic barrier.

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X. Uranin Test on the Meningeal Permeability of the Premature Infant

It is but natural that the penetrability of the hemato-encephalic barrier has been a matter of interest to numerous scientists for the purpose of determining whether foreign substances entering the blood stream can become diffused into the cerebrospinal fluid, and if so, to what extent.

Various investigators have suggested the employment of different substances for the study of this phenomenon. So Sicard (1902) recommended iodides, Mestrezat (1912) nitrates (saltpeter), Walter (1925) bromides, and Kafka (1912) uranin (fluorescein sodium).

The last mentioned substance has proved by far the superior for the purpose. It is easily, distinctly and rapidly recognizable even in very low concentrations, it is harmless to the organism, and is conveniently administered also by intramuscular injection, which is conducive to the accuracy of the dosage. In conducting experiments with small children an injection is greatly to be preferred to oral administration from the point of convenience. It furthermore removes the factor of indefiniteness which arises should the child vomit and uncertainty be created in regard to the amount of substance remaining in the body.

In fact, recent investigators (Schönfeld 1921, Jervell 1925, Feigel 1927, Leonow 1927, Esselbrügge 1929, Schippers and Peters 1929, Schaferstein 1929, Samson 1931) have exclusively employed uranin in the study of meningeal permeability.

Schönfeld conducted his tests primarily upon adult patients affected with lues of the central nervous system. In the majority

of cases he administered uranin orally (6 to 8 g.) and was able to recognize almost without any exception uranin in the central nervous system of the lues patients. With most subjects the concentration of the stain attained maximum three hours after administration. Recognition was the most rapid (one hour) in the cerebrospinal fluid of patients with progressive paralysis. As late as 17 hours after ingestion of the uranin Schönfeld was able to discern a very faint tinge in the fluid.

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JERVELL recommended uranin as a diagnostic medium in meningitic condition with children. His dosage was 0.03 g. per kilogram of body weight, chiefly administered orally. If the patient was in a bad condition or had difficulty in swallowing, intramuscular injection of a 20 per cent solution of uranin was made. A lumbar puncture was performed three hours after the administration, and distinct fluorescence was noted in all cases of meningitis.

Feigel in his studies reached the conclusion that 0.03 g. of uranin per kilogram of body weight is an excessive dosage, for the stain becomes diffused into the cerebrospinal fluid of even the majority of healthy infants and he feels that the precision of the test is interfered with. Feigel therefore regards an amount of 0.02 g. per kilogram of body weight more advisable. The punctures were made by him two and one-half hours after the administration.

Leonow carried out uranin tests on 102 children who were mormal but mostly affected with various diseased conditions. Thus, in addition to healthy children, his material comprises infant patients with, among other diseases, enteritis, pneumonia, tuberculosis, and various pathologic conditions of the central nervous system such as cerebral meningitis, encephalitis, Little's disease, epilepsy and cerebral hemorrhage. Leonow generally employed a dosage of 0.03 g. of uranin per kilogram of body weight in the form of a 15 per cent solution injected intramuscularly, except in certain cases of meningitis, in which he administered smaller doses. In all the conditions of cerebral meningitis he found a pronounced stain in the cerebrospinal fluid. This stain maintained for an exceptional length of time, in one case for over four days. From this he made the inference that in meningitic conditions not only the permeability of the hemato-encephalic barrier is increased but

also the resorption system is disturbed and the latter process greative retarded. Increased permeability was noted by Leonow also in severe cases of enteritis and in pneumonias and toxic conditions. The permeability was also elevated in a child with Little's disease and on an exceedingly high level in a case of cerebral hemorrhage. He also found the permeability to some degree elevated in healthy infants during their first year of life and particularly during the first six months. The observation was made by him in the healthy infants that age is a factor of greater significance than body weight, for even in severely atrophied children of nearly one year of age the permeability was very much lower than in high weight children about six months old.

Schippers and Peters came to the conclusion in their studies that small amounts of uranin, i.e. 0.025, 0.015 or even 0.010 g. per kilogram of body weight are preferable, for also in their opinion the use of larger amounts interferes with the precision of the test. They generally performed the lumbar puncture already one-half hour after intramuscular injection of uranin.

Schaferstein also experimented with dosage of varying amounts. At first he used 0.03 g. per kilogram of body weight, but regarding this as excessive he reduced it to 0.02 g., which he found greatly preferable in practice. He later made a further reduction to 0.015 g., which he regards as the optimum dosage. The lumbar puncture was generally made by him already forty minutes from the uranin injection. Schaferstein established that in toxic conditions of enteritis the permeability was greatly above the normal level, and he regards this an etiological factor in the causation of neurotoxic symptoms.

ESSELBRÜGGE reports that following an injection of uranin the skin and the sclerae take an intensive yellow stain already after a period of from ten to twenty minutes. It disappears from the skin in from two to nine hours, but uranin can be recognized in the urine as late as 36 hours from the injection (60 specimens of cerebrospinal fluid).

Samson states that he always employs an intramuscular dose of 0.03 g, per kilogram of body weight and performs the lumbar puncture two and one-half hours after administration. Consistently

with the findings of other investigators he ascertained a somewhat increased meningeal permeability during the first year of the infant's life and in particular during the first six months.

Personal Investigations

In my own studies I employed uranin in a dose of 0.02 g. per kilogram of body weight (cf. Methods of Investigation), administering it always as an intramuscular injection of a 20 per cent uranin solution. My cases comprise 11 premature infants on whom I performed 37 successful punctures, the specimens drawn containing no blood. One puncture only was made on four infants, always two and one-half hours after injection of the stain, on five infants it was made four times, on one six times, and on one seven times. In the latter two cases the last puncture took place 24 hours after injection. All the other punctures were generally made at intervals of one-half or one hour. The lowest birth weight of the premature infants in my uranin staining test series was 1,120 g. and the highest 1,920 g. The age of the infants at the time of puncture varies from 26 days to nine months.

As a comparison I also carried out tests with uranin on 11 full weight infants hospitalized for various diseased conditions. Thirty-eight punctures were made on these children.

Soon after the injection of uranin the skin and in particular the sclerae of all the premature infants in my material acquired a strong yellow color. With the smallest infants this occurred already one minute after injection. Several hours later the yellow color was still recognizable in the skin and sclerae of all the infants. I could not ascertain any adverse effects upon the children from the use of the stain and there was no disturbance in the normal increase in weight following the punctures.

The results of my investigations will be seen from Table 17, in which the children are numbered consecutively according to age at the time of puncture. The age has been rounded out to the nearest full month. To avoid confusion with the main series used in my investigations the uranin test material is numbered from 101 upward. The figure given in the column captioned Dilution

TABLE 17
Uranin Test in Premature Infants
Author's Investigations

Case No.	Age, months	Weight at Birth, grams	Weight at Puncture, grams		Interval from Uranin Injection, hours	Dilution Coef- ficient
101	1	1,340	1,790	12	1/2	0+
					1	4
					1 1/2	6
					2	5
102	2	1,830	2,270	8	1/2	1
					1	5
					1 1/2	5
					2	4
					6	3
					20	0+
					24	0±
103	2	1,410	2,950	8	2 1/2	5
104	3	1,570	2,900	12	1	3
					1 1/2	5
					2	6
					2 1/2	5
105	3	1,700	3,500	6	1/2	1
					1	5
					1 1/2	4
					2	4
106	3	1,600	3,460	7	2 1/2	4
107	4	1,820	4,700	2	1/2	1
					1	5
					1 1/2	4
					2	4
108	4	1,850	4,110	5	1/ 72	0+
					1	3
					1 1/2	4
					2	3
					6	3
					24	0+
109	6	1,120	4,430	1	1/2	1
					1	3
					1 1/2	3
					2	4
110	9	1,920	7,420	4	2 1/2	3
111	9	1,700	4,860	1	2 1/2	3

Coefficients indicates the last dilution of cerebrospinal fluid with an equal amount of distilled water which still is fluorescent. If $_{no}$ fluorescence was seen in the first dilution the sign + will indicate that the undiluted fluid was fluorescent.

Case

No.

112

114

116

117

118

119

120

121

122

It will be seen from this tabulation of the results of my own investigations that uranin given to premature infants is conveyed into the cerebrospinal fluid to a very great extent and within a relatively short time. This is an indication of exceedingly great meningeal permeability in premature infants. Another observation worthing of notice is in my opinion the decrease which sets in fairly soon in the concentration of uranin in the cerebrospinal fluid. In numerous cases a lower concentration is already found at the puncture reade two hours after injection than in the preceding puncture.

For comparison, the uranin test results obtained by the same method from the full weight children are similarly tabulated in Table 18.

In this material of full weight children a high meningeal permeability is found only in the case of a child affected with tuberculous meningitis. With infants under one year I found, corroborating the findings of other investigators, that some amount of uranin is conveyed into the cerebrospinal fluid but that this amount is considerably smaller than in the case of premature infants. I regard case No. 112 as particularly striking. The child's weight at the time of puncture was not more than 3,210 g., yet the dilution coefficient did not exceed 1 in any of the four punctures made. With premature infants of the same age and about the same weight I found a dilution coefficient of from 4 to 6.

By means of these uranin tests it has been possible for me to also obtain experimentally proved evidence of an extremely high meningeal permeability in premature infants. Thus I have obtained the support of experiment to the opinion expressed by me above in several connections that many of the deviations from the normal found by me in the properties of the cerebrospinal fluid of the premature infant are chiefly produced by an increased meningeal permeability in the premature infant.

TABLE 18
Uranin Test in Full Weight Children
Author's Investigations

Case No.	Age, months	Weight, at Birth, grams	Weight at Puncture, grams	No. of Cells per cmm.	Interval from Uranin Injection, hours	Dilution Coef- ficient	Diagnosis
112	3	3,120	3,210	0	1 1 1 1 2 2 2 2 1 2 3	0+ 1 1 1 0+	Atrophia
113	4	3,440	4,860	2	1 1 1 1 ₂ 2 2 1 ₂	1 1 1	Gastro- enteritis ac.
114	5	3,360	7,330	0	$1\frac{1}{2}$ $2\frac{1}{2}$		Enteritis ac.
115	7	3,400	8,080	110	1 1 1/2 2 1/2 6	4 6 5 5 3	Meningitis tuberculosa
116	9	3,200	8,940	1	1 1 1 1 2 2 2 1 2 3	1 1 2 0+	Pyelitis ac.
117	10	3,100	8,400	1	1 1 ½ 2 2 ½	0+ 1 0+	Otitis med. supp.
118	13	4,000	11,750	0	1 2 2 ½		Broncho- pneumonia
119	13	3,700	9,380	0	$1 \\ 1 \frac{1}{2} \\ 2 \\ 2 \frac{1}{2}$	0+ 0+ 0+	Enteritis ac.
120	15	3,300	7,790	1	2 1/2	0+	Enteritis ac.
121	24	3,000	9,900	0	1 ½ 2 ½	_	Otitis med.
122	47	3,200	16,500	0	1 2 2 ½	_	Asthma bronchiale

XI. Some Minor Observations on the Properties of the Cerebrospinal Fluid of the Premature Infant

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I was unable to find any correlation between the amount of physiological reduction in weight in the premature newborn infant (in my material from 3 to 23 per cent) and the cell and protein contents of the cerebrospinal fluid in cases where the weight, following the reduction, soon began to rise. Where on the other hand the weight maintained the low level for some length of time I uniformly made a finding of relatively high amounts of cells and protein. At the same time the vital functions of such premature children were very low in several respects, they are poorly, had a great tendency to subnormal temperature and also frequently were cyanotic.

With these premature infants the cerebrospinal fluid drained post mortem was sometimes tound to have a very high protein content. In one of these cases, dying at the age of eleven days, the protein content was 325 mg. per cent. This specimen of fluid naturally is not included in my material, but I have the specimen withdrawn from the same child at the age of one day, which contained 112 mg. per cent of protein (case No. 7). Accordingly the protein concentration had increased greatly within ten days. On the whole, however, I have not found the fluid obtained from premature infants post mortem to greatly differ from that withdrawn in vivo, even if some small increase in the cell and protein contents are common.

In all the cases of premature infants punctured by me at the Helsinki Municipal Epidemic Hospital a full blood picture was

taken at intervals of two weeks. I could establish no interrelation between the alterations in the blood picture and fluctuations in the amounts of cells and protein in the cerebrospinal fluid. Not even severe anemia had any effect on the properties of the fluid, these always maintaining their own course. Also this circumstance demonstrates that the brain of the premature infant follows its own laws of development, as in the phenomenon of megacephalus mentioned above (Ylppö).

Even if I encountered fairly high amounts of protein in the cerebrospinal fluid of the premature infant I was in no instance able to find so-called cobweb formation in stagnant fluid.

No differences could be ascertained by me in the properties of the cerebrospinal fluids withdrawn from premature infants of the male and female sex.

XII. Summary and Conclusions

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In this study I have performed a total of 200 lumbar panetures on 100 healthy premature infants. I have further performed 37 lumbar punctures on 11 premature infants following an intramuscular injection of uranin, and 38 lumbar punctures on 11 full weight children under similar conditions.

The answers obtained in these investigations to the questions which I had set when proceeding to conduct the tests are briefly stated in the following.

- 1. A. The withdrawal of cerebrospinal fluid from the premature infant by lumbar puncture is an entirely successful procedure.
- B. I have withdrawn from premature infants at one puncture amounts varying from 3 to 8 cc. No adverse effects from this upon the development of the premature child have been noted, and I therefore regard the performance of a lumbar puncture upon premature infants as fully harmless.
- C. Cerebrospinal fluid is present in the small premature infant in amounts varying from about 10 to about 20 cc., and in the larger premature infants in amounts from about 20 to about 30 cc.
- 2. A. With the exception of two cases all the specimens of cerebrospinal fluid collected by me were clear. Microscopic examination revealed that the slight turbidity occurring in these two specimens was due to the presence of red blood cells. Blood-tinged cerebrospinal fluid specimens thus were present in my material in 2 per cent of the cases.

- B. The cerebrospinal fluid of the newborn premature infant is almost regularly yellow or yellowish. I have frequently found a yellow coloring in the cerebrospinal fluid of the premature infant as late as the second month of life. At least to a major extent this color is produced by bilirubin. The latter substance becomes diffused into the cerebrospinal fluid from the blood chiefly by means of the meningeal permeability, which is increased in a marked degree in the premature infant. However, cerebral hemorrhage occurring sub partu may also tend to increase the bilirubin content of the cerebrospinal fluid.
- C. In numerous cases it may be possible to regard as probable, by evaluation of the appearance of the cerebrospinal fluid and by the results of investigations related thereto, that cerebral hemorrhage has occurred at delivery, but definite inference of the presence or absence of such hemorrhage cannot be made by this means in by far all the cases.
- 3. A. The cell count and the amount of protein in the cerebrospinal fluid of the premature infant are considerably higher than those in the normal fluid and moderately higher than even those in the fluid of the full weight newborn infant.
- B. With premature infants of a low weight at birth the cell count and the amount of protein in the cerebrospinal fluid are higher and maintain the elevated level for a longer period of time than those of premature infants with a higher weight at birth. The protein concentration of the cerebrospinal fluid of the small premature infant sometimes exceeds the normal also during the second six month period of life and even at the age of one year.
- C. As the primary cause of the elevated cell and protein concentrations which I obtained in the premature infants I regard the great increase in the meningeal permeability in these children. At the same time, however, I consider it very probable that in certain cases the elevated cell and protein concentrations are augmented by a condition caused by cerebral hemorrhage which has occurred subpartu.

- 4. On the basis of the results of the tryptophan and mastic reactions carried out by me I regard it as very probable that the proteins present in the cerebrospinal fluid of the premature infant frequently differ qualitatively to some extent in the first month of life and particularly in the newborn period from the proteins found in the cerebrospinal fluid in later life.
- 5. I have found the sugar values in the cerebrospinal fluid of the premature infant to be fairly high and on an approximate level with the blood sugar values determined simultaneously. I regard the increased meningeal permeability in the premature infant as the principal reason for these values.

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6. Following an intramuscular injection of uranin I have noted that the diffusion of the stain into the cerebrospinal fluid of the premature infant is considerably more rapid and greater in amount than with the full weight infants of my control material. I thus have been able to demonstrate also by experimental work that the premature infant has a very greatly increased meningeal permeability.

XIII. Zusammenfassung und Schlussfolgerungen

Es wurden für 100 gesunde Frühgeburten insgesamt 200 Lumbalpunktionen ausgeführt. Ausserdem habe ich nach einer intramuskulären Uranininjektion für 11 Frühgeburten denselben 37 Lumbalpunktionen samt ebenfalls nach einer Uranininjektion für 11 ausgetragene Kinder 38 Lumbalpunktionen gemacht.

Die Antworten auf die von mir vorgelegten Fragen sind nach meinen Untersuchungen in aller Kürze folgende:

- 1. A. Das Erhalten des Liquor cerebrospinalis aus dem Frühgeburten mit der Lumbalpunktion gelingt ausgezeichnet.
- B. Ich habe aus den Frühgeburten 3—8 ccm Liquor cerebrospinalis auf einmal herausgenommen. Dieses habe ich die Entwicklung des Frühgeburten in keiner Weise beschädigt zu haben festgestellt, aus welchem Grunde ich die Ausführung der Lumbalpunktion dem Frühgeburten für gefahrlos halte.
- C. Die Menge des Liquor cerebrospinalis beträgt bei kleineren Frühgeburten etwa 10—20 ccm und bei grösseren etwa 20—30 ccm.
- 2. A. Ausser. 2 Fällen sind alle Spinalflüssigkeiten klar gewesen. Bei einer mikroskopischen Untersuchung zeigte sich in diesen 2 Spinalflüssigkeiten eine schwache Trübung durch rote Blutzellen veranlasst. Es sind von meinem Material also 2% blutenthaltende Spinalflüssigkeiten.
- B. Die Spinalflüssigkeit des neugeborenen Frühgeburten ist beinahe regelmässig gelb oder gelblich. Gelbe Farbe habe ich in der

Spinalflüssigkeit der Frühgeburten oft noch auch während des zweiten Lebensmonates festgestellt. Die Farbe ist wenigstens hauptsächlich durch Bilirubin verursacht. Dieses wandert in die Spinalflüssigkeit aus dem Blute vorzugsweise infolge der bedeutend erhöhten meningeaten Permeabilität bei den Frühgeburten, es kann aber in einigen Fällen eine eventuelle Gehirnblutung bei der Geburt auf die Bilirubinmenne einigermassen erhöhend wirken.

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- C. Bei vielen Fällen kann man auf Grund des Ausseheits der Spinalflüssigkeit und durch die sozusagen damit verbundenen Untersuchungsmethoden erhaltener Untersuchungsergebnisse für wahrscheinlich halten, dass bei der Geburt eine Gehirnblutung vorgekommen ist, aber einstweilen ist es bei weitem nicht immer möglich durch die gebräuchlichen Methoden mit Sicherheit fistzustellen, ob eine Blutung vor sich gegangen hat oder nicht.
- 3. A. Die Zellen- und Eiweissstoffmengen in der Spinalflüssigkeit eines neugeborenen Frühgeburten sind bedeutend grösser als die Zellen- und Eiweissstoffmengen des normalen Liquors und ansehnlich grösser als die des Liquors eines ausgetragenen neugeborenen Kindes.
- B. Bei den Frühgeburten mit kleinerem Geburtsgewicht sind die Zellen- und Eiweissstoffmengen grösser und verbleiben grösser als die normalen Mengen eine längere Zeit als bei den Frühgeburten mit grösserem Geburtsgewicht. Die Eiweissmenge in der Spinalflüssigkeit des Frühgeburten mit kleinerem Geburtsgewicht übersteigt bisweilen die normale Menge noch während des zweiten Halbjahres und bisweilen sogar im Alter von einem Jahre.
- C. Für den wichtigsten Grund der von mir festgestellten grösseren als die normalen Zellen- und Eiweissmengen halte ich die bei den Frühgeburten bedeutend erhöhte meningeale Permeabilität. Gleichzeitig halte ich jedoch für sehr wahrscheinlich, dass in einigen Fällen zur Erhöhung der Zellen- und Eiweissmengen eine bei der Geburt eventuelt vorgekommene Gehirnblutung beigetragen hat.
- 4. Auf Grund der mit Tryptophan- und Mastixreaktionen erhaltenen Untersuchungsergebnisse halte ich für sehr wahrscheinlich.

dass die Eiweissstoffe in der Spinalflüssigkeit eines Frühgeburten während des ersten Lebensmonats und besonders bei den neugeborenen Frühgeburten oft in ihrer Qualität einigermassen von den Eiweissstoffen eines späteren Alters abweichen.

- 5. Die Zuckerwerte in der Spinalflüssigkeit des Frühgeburten habe ich ziemlich hoch und im Vergleich zu den gleichzeitig genommenen entsprechenden Zuckerwerten des Blutes ungefähr auf derselben Höhe stehend festgestellt. Den hauptsächlichen Grund zu den von mir konstatierten hohen Zuckerwerten der Spinalflüssigkeit will ich in der erhöhten Permeabilität bei den Frühgeburten sehen.
- 6. Nach intramuskulären Uranininjektionen habe ich festgestellt, dass Uranin in die Spinalflüssigkeit des Frühgeburten bedeutend schneller und in bei weitem grösserer Menge wandert als bei den ausgetragenen Kindern meines Vergleichsmaterials. Mithin habe ich auch experimentell beweisen können, dass die Frühgeburten bedeutend erhöhte meningeale Permeabilität besitzen.

XIV. Résumé et Conclusions

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Nous avons pratiqué à 100 avortons sains en tout 200 ponctions lombaires. De plus nous avons, après une piqûre intramusculaire d'uranine, éxécuté 37 ponctions lombaires chez 11 avortons et 38 ponctions lombaires chez 11 enfants normaux.

Les réponses aux questions posées par nous sont sur base de mes recherches précédentes brièvement les suivantes:

- 1. A. Obtention du liquide rachidien d'un avorton par ponction lombaire réussit extrèmement bien.
- B. Nous avons pris des avortons 3—8 cm³ du liquide rachidien par fois. Nous n'avons pas pu constaté que cela aurait eu une influence nocive au avorton, de sorte que nous considèrons la ponction lombaire comme une opération sans danger au avorton.
- C. La quantité du liquide rachidien des avortons plus petits est env. 10-20 cm³ et celle des avortons les plus grands est env. 20-30 cm³.
- 2. A. Sauf deux échantillons tous les liquides rachidiens ont été clairs. La microscopie a montré un léger trouble dans ces deux liquides, provenant des globules rouges. Dans mes cas il y a donc 2% d'observations à liquides rachidiens contenant du sang.
- B. Le liquide rachidien d'un avorton nouveau-né est presque régulièrement jaune ou jaunâtre. Nous avons constaté une nuance jaune dans le liquide rachidien de l'avorton souvent même dans son troisième mois de la vie extrauterine. Cette couleur devient au moins principale-

ment du bilirubine; ceci est conduit au liquide rachidien du sang, principalement à cause de la permeabilité considérablement augmentée des méninges chez les avortons, mais dans quelques cas l'hémorrhagie cérébrale pendant l'accouchement peut influer dans une certaine mesure sur la quantité du bilirubine dans le liquide rachidien.

- C. Dans un grand nombre de cas on peut supposer la présence d'une hémorrhagie cerébrale obstétricale en se basant sur l'éxamen du liquide rachidien mais jusqu'à nouvelle ordre une constatation certaine n'est pas possible sans autopsie.
- 3. A. Les quantités de globules et de l'albumine dans le liquide rachidien d'un avorton nouveau-né sont largement supérieures à celles du liquide normal et même considérablement supérieures à celles du liquide d'un nouveau-né à terme.
- B. Les avortons d'un moindre poids de naissance ont des quantités de globules et de l'albumine supérieures à celles des avortons d'un poids plus grand de naissance et aussi elles restent supérieures aux normales un plus long temps. La quantité d'albumine dans le liquide rachidien d'un avorton d'un moindre poids de naissance est quelques fois supérieure pendant normale même à le six mois et parfois jusqu' à l'âge d'un an.
- C. Nous considèrons comme raison principale pour les quantités de globules et de l'albumine que nous avons constatées supérieures aux normales le perméabilité des méninges notablement augmentée des avortons. Nous trouvons cependant très vraisemblable, que l'influence de l'hémorrhagie cérébrale dans l'accouchement augmente dans quelques cas la quantité de globules et de l'albumine dans le liquide rachidien.
- 4. Sur base des résultats de recherches au quels nous sommes arrivé par les réactions de tryptophan et de mastix nous trouvons bien probable que l'albumine dans le liquide rachidien d'un avorton dans son premier mois et surtout chez les nouveau-nés se diffère souvent en qualité dans quelque mesure de celle d'un âge plus avancé.
- Nous avons constaté que les quantités du sucre au liquide rachidien d'un avorton sont assez hautes et sont bien comparable

avec les valeurs du sucre sanguins correspondantes. Nous considérous la raison principale pour les valeurs assez hautes du sucre dans le liquide rachidien, la perméabilité augmenté des méninges des avortons.

Case

No.

13

14 15

6. Après une piqûre intramusculaire d'uranine nous avons constaté que la conduite de cette substance au liquide rachidien est considérablement plus vite et plus abondante chez les avortons que chez enfants normales dans le groupe de comparaison. Nous avons ainsi pu démontrer aussi par la voie expérimentale que les avortons ont une perméabilité des méninges considérablement augmentée.

XV. Table of Certain Test Results

TABLE 19

Case No.	Age,	Weight at Birth, grams	Weight at Punc- ture, grams	Cell count per cmm.	Erythro- cyte count per cmm.	Protein, mg %	Trypto- phan Reaction	Fluid Sugar, mg %	Blood Sugar mg %
1	3 24	1410	1370	5	1	106		0.0	
	14		1380	12	6	106	+	66	
	28		1640	25	0	81		78	
2	12/24	1330	1300	6	0	113		68	64
3	13,24	1580	1550	4	0	138	+		
4	16/24	920	900	15	139	75	+		
5	25/24	900	890	5	860		+		
6	1	1300	1260	9	5	138	+		
7	1	1320	1300	7	11	113	+		
8	1	2000	1830	4	11	113	+		
	17		2040	3	0	75	7	72	4745
	31		2400	5	0	63		12	62
	45		2840	6	0	69			
	59	1	3280.	4	0	44	i		
	73		3550	3	0	38		78	
	87		4070	2	9	94		60	
	101		4450	1	0	69		78	00
9	2	1700	1650	10	37	50		74	96
1	16		1680	13	2	75		14	78
	30		2100	17	53	75			
	14		2390	8	1	63			
10	3	1825	1750	14	2	63			
	16		1970	1	0	63		78	mes
	30		2320	2	0	56		10	72
	-14		2660	1	0	38			
	58		2940	3	1	25			
1	4	1570	1390	11	35	113	+	70	78
	20		1360	31	3	131		74	/8
	34		1430	39	0	138		80	
	48		1800	32	1	138		78	- 1
2	4	1770	1600	4	1	88		18	
3	4	1950	1770	8	29	113	+		
1	24		1810	11	0	113		64	
	47		2350	3	0	50		64	
	4	2250	2040	8	0	75	+	04	
- 1	16		1700	14	6	100	T		
	5	1600		18	170			ine	90
	19		1740	7	0	56		106	80

TABLE 19 (Cont.)

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Case No.	Age, days	Weight at Birth, grams	Weight at Punc- ture, grams	Cell count per cmm.	Erythro- cyte count per cmm.	Protein, mg %	Trypto- phan Reaction	Fluid Sugar, mg %	Blood Sugar, mg %
15	33		2090	6	2	31		90	
	47		2570	7	1	44	į l	88	
	61		2980	5	3	50		80 70	
16	5	1690	1560	13	39	106	+	70	
	21		1940	4	0	69	±	94	
	39		2340	9	4	63		94	80
	53		2670	6	1	56			
- 1	63		2850	9	4	56			
	82		3340	6	1	38			
17	5	2140	1830	8	4	125			
18	5	2150	2060	16	0	75		96	100
	19		2320	6	2	50			100
	33		2750	6	0	31		76	- 11
	47		3270	3	0	44		76	
	61		3620	2	1	44		80	
19	6	1820	1750	8	1	100	+	1	
	24		2160	5	0	69	± 1	68	80
	42		2560	6	3	81	_	00	- QU
	56	1	2990	8	3	63		- 1	
	70		3370	4	25	50			
20	6	1970	1900	10	5	100	+	1	
	22		2200	8	37	69	+	66	60
	37		2540	6	7	69	±	00	90
1	51	1	2860	6	2	63	_		
	65	1	3240	4	2	31			
	79		3420	11	0				
	93		3770	3	1	38		80	
1	7	1900	1380	15	5	100			
2	8	1850	1600	8	4	106		86	80
	22		1840	8	3	100			
	36	İ	2300	10	2	63			
	64		2550	7	0	63		75	
3	8	1920	1670	8	0	81	+		
	25		1980	10	9	106			
	40		2380	6	2	88	±	88	84
	55		2760	4	1	63	+		
	69		2980	9	1	50			
	83	,	3370	6	0	63			
1	101		4210	8	1	44			4

TABLE 19 (Cont.)

Case No.	Age, days	Weight at Birth, grams	Weight at Punc- ture, grams	Cell count per cmm.	Erythro- cyte count per cmm.	Protein, mg %	Trypto- phan Reaction	Fluid Sugar, mg %	Blood Sugar mg %
24	9	1775	1370	44	27	400			
25	9	2280	2120	5	460	138	_		
26	10	1300	1150	36	2	163			
27	10	1820	1690	10	1	100			
	24		1890	6	0		±	90	82
	38		2310	5	1	63 75			
	52		2600	8	0	56			
	66		2950	3	0	56			
	80		3380	2	1	44		70	
28	10	2050	1680	3	1	75		84	
29	10	2090	2120	4	3	50			
30	11	1300	1130	13	1	188		1	
31	12	1760	1800	7	0	69			
	26		2110	5	0	63	-		
	42	1	2590	3	0	63	1	00	
	57		2870	2	1	.50		62	78
	71		3090	2	1	56			
	85		3470	0	2	25	1		
32	14	1700	1760	11	0	269			
33	14	1770	1560	23	0	138			
34	14	1880	1580	5	17	213			
35	14	2300	2180	4	0	213			
36	17	1600	1790	10	1	106		72	
	31		2100	10	3	69		62	75
	45		2090	17	1	69		96	
37	17	1750	2000	3	0	75		90	
	64		3000	1	0	25		98	- 1
8	18	1160	730	11	1	125		90	
9	19	2140	2070	8	0	69	+	86	92
	34		2360	5	41	63		00	92
	44		2610	6	0	63			1
	68		3470	5	1	38			
	82		3540	10	0	25		74	
	19	2210	2230	8	0	75	+	86	90
	34		2600	6	2	63	_	00	30
1	14	1 :	2960	8	1	75			
	30	4	1220	7	0	31		-	
1 2	21	1450 1	1650	9	2	50		75	

TABLE 19 (Cont.)

Case No.

Case No.	Age, days	Weight at Birth, grams	Weight at Punc- ture, grams	Cell count per cmm.	Erythro- cyte count per cmm.	Protein, mg %	Trypto- phan Reaction	Fluid Sugar, mg %	Hood Sigar, me o
42	21	1900	1860	6	2	69			
43	27	2000	2370	4	3	63			
44	27	2500	2840	5	1	69			
45	28	2400	2510	4	8	31			
46	28	2480	2750	5	0	31		84	711
47	30	1530	1790	8	0	75			
48	32	1530	1850	12	0	69	±		
	45		2220	5	1	44		İ	1
	61		2800	3	5	75		60	
	76		3170	1	0	75		90	62
	90		3490	4	0	75			
49	33	1810	1690	15	0	63			1
50	33	2050	1810	4	0	38	±	80	
	56		2380	5	0	44	T	80	
51	34	1980	2340	7	10	63		017	
52	37	1780	1920	4	11	88		-	1
53	39	2260	2470	7	4	63	_		
	53		2700	3	0	75		80	65
54	44	1120	1450	15	4	100	±	(317	1112
	59		1750	5	0	94	-da	70	82
	84	1	1920	9	1	94			
	102	1	1910	7	2	69	1	Î	
	117	1	2390	8	0	69			
	131		2740	2	0	50		68	
	145		2930	10	1	69		1717	
	159		3460	3	0	63			
5	44	1480	1700	5	1	75	_		
	76		1680	5	0	56			- 11
	110		2080	2	0	25			- 11
6	44	2400	2750	3	0	25		88	120
7	45	1500	2490	8	2	69	±		
	132	-	4730	10	0	38			
8	47	1500	1680	10	0	113			
	78		2300	6	23	63	_		
9	47	1550	2080	17	0	100			
	60		2390	7	1	94			
	76		2880	13	4	81		78	66
	91		3150	2	27	63			

TABLE 19 (Cont.)

lase No.	Age,	Weight at Birth, grams	Weight at Punc- ture, grams	Cell count per cmm.	Erythro- cyte count per cmm.	Protein, mg %	Trypto- phan Reaction	Fluid Sugar, mg %	Blood Sugar mg %
		1250	2020	7		000			
60	47	1750	3070	3	4 0	88	土		
	78	2100	2960	8	4	69 50	-		
61	49 64	2100	3400	7	1	31			
	82		3870	4	0	44		80	68
00	49	2300	3530	3	170	44		00	00
62	52	2250	2080	3	1	44			
63	121	2230	2880	0	0	19	-		
	55	1850	2680	3	0	56			
64 65	56	1730	2190	5	1	44			
66	59	2200	2790	4	0	44			
67	63	1400	2200	6	0	50			
68	64	1500	3100	8	2	38		72	
69	65	1670	2340	9	2	69		12	
70	67	1645	2680	12	0	75			
71	70	1650	2270	4	1	69			
72	72	1000	1350	12	1	69			
73	74	1400	2950	9	40	09			
74	75	1970	3520	7	1	38			
75	82	1550	2600	5	7	30			
76	91	1350	2750	2	1	63			
10	160	1350	3620	3	0	38		78	
77	91	1400	1760	4	0	38		10	
78	108	1630	2690	3	0	31			
79	121	2250	1910	2	0	38			
80	135	1050	2200	5	1	44			
00	178	1000	2760	4	0	44			
81	143	2100	5050	2	0	44		1	
82	148	2500	5160	2	0	19		1	
83	159	2400	4000	1	1	63			
84	171	1820	5210	1	0	25			
85	194	2100	6800	2	0	44		78	
86	198	2250	6210	4	0	38		10	
87	229	1750	5990	2	0	31			68
88	247	2120	7580	4	143	31			00
89	252	2400	6700	0	0	19			
90	257	1700	4800	1	0	25			
91	267	1500	6530	1	0	19			

TABLE 19 (Cont.)

Case No.	Age, days	Weight at Birth, grams	Weight at Punc- ture, grams	per	Erythro- cyte count per cmm.	Protein, mg %	Trypto- phan Reaction	Fluid Sugar, mg %	Blood Sugar, mg %
92	271	1600	6600	0	0	31	_		
93	273	1300	6240	1	0	31			
94	274	1130	5400	3	0	31			
95	276	1890	6400	2	0	31			
96	370	1750	9560	2	1	44			
97	388	2200	5890	1	2	31	_		
98	468	2400	8500	2	0	25		68	
99	495	1600	5160	1	0	25			
100	500	2350	9980	0	0	19			

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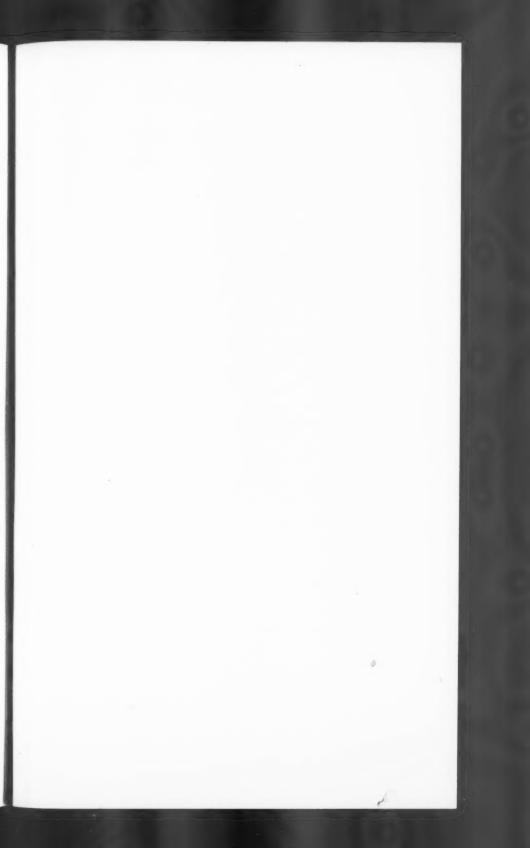
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